Swallowing difficulties in Friedreich ataxia

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Submitted in total fulfilment of the requirements of the degree of Doctor of Philosophy

April 2017

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Abstract

Swallowing is an important biological function reliant on the coordinated interaction between motor and sensory mechanisms. Swallowing dysfunction (dysphagia) is a common sequela of neurodegenerative disease and is associated with significant morbidity and mortality. Dysphagia is associated with malnutrition, dehydration, and aspiration-related pneumonia, and psychological issues such as reduced self-esteem and social isolation. For individuals with movement disorders, dysphagia can be exacerbated by concurrent upper limb impairment, making it difficult to feed independently.

Friedreich ataxia (FRDA) is an autosomal recessive condition resulting in a deficiency of frataxin, most commonly due to homozygosity for a GAA trinucleotide repeat expansion in intron 1 of *FXN*. FRDA manifests in widespread central and peripheral nervous system degeneration, as well as impairment of the cardiac, skeletal, and endocrine systems. Pneumonia (a common implication of dysphagia) is the cause of death in approximately 10% of individuals with FRDA. Whilst dysphagia is a widely accepted feature of FRDA, understanding of the underlying mechanisms and characteristics of dysphagia in FRDA is limited.

This project (and resulting thesis) sought to investigate and characterise the swallowing function of individuals with FRDA suspected of having dysphagia, and document the frequency of concomitant aspiration in this cohort. It was also aimed to determine relationship between oropharyngeal dysphagia and clinical markers of FRDA, including age at time of disease onset, disease duration, the GAA repeat size on the smaller (GAA1) and larger (GAA2) *FXN* allele. Predictors of aspiration in this cohort were also explored. In addition the psychosocial implications of dysphagia were considered using a standardised questionnaire. The study was largely cross-sectional in design, with a smaller group of individuals with FRDA receiving a 12 month follow up to investigate the relationship between dysphagia and disease progression.

Results confirm oropharyngeal dysphagia with concomitant aspiration is present in individuals with FRDA and worsens with disease duration and severity. Aspiration in this population can occur at any time during the course of the disease, and therefore swallowing function should be monitored closely. Dysphagia was also shown to significantly affect the quality of life of individuals with FRDA compared to a group of healthy controls. The clinical implications of these findings are discussed along with future directions.

Thesis with publication

This thesis includes one publication:

Keage, M., Delatycki, M., Corben, L., & Vogel, A. (2015). A systematic review of self-reported swallowing assessments in progressive neurological disorders. *Dysphagia*, *30*(1), 27-46.

Submitted with this thesis are the co-author authorisation forms of Professor Martin Delatycki, Dr Louise Corben, and Dr Adam Vogel.

Ms Keage contributed to the design of the study, collection, analysis and interpretation of the data, and drafting and revising the manuscript for intellectual content.

Professor Delatycki contributed to the design of the study, analysis and interpretation of the data, revising the manuscript for intellectual content, and supervision of the student.

Dr Corben contributed to the design of the study, analysis and interpretation of the data, revising the manuscript for intellectual content, and supervision of the student.

Dr Vogel contributed to the design of the study, collection, analysis and interpretation of the data, revising the manuscript for intellectual content, and supervision of the student.

Declaration

This is to certify that:

I. The thesis comprises only my original work towards the PhD except where indicated in the Preface,
II. Due acknowledgements has been made in the text to all other material used,
III. The thesis is less than 100,000 words in length, exclusive of tables, maps, bibliographies and appendices.

Preface

This doctoral thesis conforms to the referencing style recommended by the American Psychological Associations Publication Manual (6th edition).

The research was completed from April 2012 to May 2016 and primarily conducted at the Monash Medical Centre, Melbourne. Data was also collected via visits to the participants' homes and at the Kingston Centre, Melbourne, where participants were admitted for inpatient rehabilitation.

The research was supervised by Associate Professor Adam Vogel (Head of the Centre for Neuroscience of Speech, Department of Audiology and Speech Pathology, The University of Melbourne, Australia, Department of Neurodegeneration, Hertie Institute for Clinical Brain Research, Eberhard Karls Universität Tübingen, Germany), Professor Martin Delatycki (Bruce Lefroy Centre for Genetic Health Research, Murdoch Childrens Research Institute, Melbourne, Australia, Clinical Genetics, Austin Health, Melbourne, Australia), Dr Louise Corben (Bruce Lefroy Centre for Genetic Health Research, Murdoch Childrens Research Institute, Melbourne, Australia, School of Psychological Sciences, Monash University, Melbourne Australia, and Monash Health, Australia), and Associate Professor Gary Rance (Department of Audiology and Speech Pathology, The University of Melbourne, Australia).

Financial support was provided by the National Health and Medical Research Council of Australia (APV holds a Career Development Fellowship ID 1082910, and the Australian Government (MK holds an Australian Post Graduate Award), and The University of Melbourne.

Acknowledgements

First I wish to acknowledge the patients and families at the Friedreich Ataxia Clinic (Melbourne) for so willingly participating in this study. I have been humbled and touched by your stories, challenges and triumphs. Thank you.

My sincere gratitude and thanks goes to Associate Professor Adam Vogel for his mentorship, support and patience. Adam has challenged me to be a better researcher, thinker, educator and clinician. Thank you Adam.

I am indebted to Professor Martin Delatycki and Dr Louise Corben for supporting me through this process. I am inspired by your relentless passion, drive, and commitment to improve the lives of people living with Friedreich ataxia. In addition I wish to thank Associate Professor Gary Rance for sharing his knowledge and expertise

Thank you Associate Professor Bronwyn Davidson for valued support and encouragement through this process.

I could not imagine a better environment to do a PhD than The Centre for Neuroscience of Speech at The University of Melbourne. Thanks to all for the peer support and comic relief. I hope to work with you all for many, many years to come.

Thank you to Professor Richard Dowell, Professor Angela Morgan, and the team at the Department of Audiology and Speech Pathology at The University of Melbourne. I feel very lucky to work within such a supportive environment.

Thanks to Matthew Poole, Isabelle Ott and Jessamy Dyer who generously donated their time to interpret the assessments used in this research.

Thanks Mum, Dad, Hannah, Owen, Hazel, Genevieve, Jocelyn and Tim for your encouragement, hugs, and free meals.

I would not be at this point without my partner Bilal. Thanks Billy for always reassuring me that everything would be ok!

I wish to acknowledge the National Health and Medical Research Council of Australia, the Australian Government, and The University of Melbourne for financial and administrative support.

Contents

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Abbreviations

ARSACS: Autosomal recessive spastic ataxia of Charlevoix-Saguenay

AT: Ataxia-Telangiectasia

BARS: Brief Ataxia Rating Scale

CADN: Clinical Assessment of Dysphagia in Neurodegeneration

cMRI: Cardiac Magnetic Resonance Imaging

CN: Cranial Nerve

CNS: Central Nervous System

DDK: Diadochokinetic

DegHI: The Deglutition Handicap Index

DHI: The Dysphagia Handicap Index

DQ: Dysphapark Questionnaire

DRG: Dorsal Root Ganglion

DYMUS: The Dysphagia in Multiple Sclerosis Questionnaire

EAT-10: Eating Assessment Tool

EKG: Electrocardiography

FAIS: Friedreich Ataxia Impact Scale

FARR: Friedreich Ataxia with Retained Reflexes

FARS: Friedreich Ataxia Rating Scale

FDA-2: Frenchay Dysarthria Assessment (second edition)

FEES: Fibreoptic Endoscopic Evaluation of Swallowing FIM: Functional Independence Measure

fMRI: Functional Magnetic Resonance Imaging

FRDA: Friedreich ataxia

FXN: Frataxin gene

GAA: Guanine-Adenine-Adenine

HDAC: Histone Deacetylase

ICARS: International Cooperative Ataxia Rating Scale

ICC: Intraclass Correlation Coefficient

LMN: Lower Motor Neuron

LOFA: Late Onset Friedreich Ataxia

LSVT: Lee Silverman Voice Technique

MBI: Modified Barthel Index

MBSImp: Modified Barium Swallow Impairment Profile

MEG: Magnetoencephalography

MICARS: International Cooperative Ataxia Rating Scale

MRI: Magnetic Resonance Imaging

MS: Multiple sclerosis

MSA: Multisystem Atrophy

MSA-C: multiple system atrophy-cerebellar type

PD: Parkinson's disease

PET: Positron Emission Tomography

PNS: Peripheral Nervous System

QOL: Quality of life

RLS: Restless Leg Syndrome

ROMPO: Radboud Inventory for Parkinson's disease

RT: Reaction Time

SARA: The Scale for the Assessment and Rating of Ataxia

SDQ: Swallowing Disturbance Questionnaire

SES: Surface electrical stimulation

SSQ: Sydney Swallow Questionnaire

Swal-QOL: Swallowing Quality of Life Questionnaire

TMS: Transmagnetic Stimulation

UMN: Upper Motor Neuron

UTI: Urinary Tract Infection

VFSS: Videofluoroscopic Study of Swallowing

VLOFA: Very Late Onset Friedreich Ataxia

WHO: World Health Organization

Peer reviewed publications and presentations

Publications

Keage, M., Delatycki, M., Gupta, I., Corben, L., & Vogel, A. (2016). Dysphagia in Friedreich Ataxia. (*Under review*).

Vogel, A. P., **Keage, M. J.**, Johansson, K., & Schalling, E. (2015). Treatment for dysphagia (swallowing difficulties) in hereditary ataxia. *Cochrane Database Syst Rev, 11, Cd010169.* doi:10.1002/14651858.CD010169.pub

Keage, M., Delatycki, M., Corben, L., & Vogel, A. (2015). A systematic review of self-reported swallowing assessments in progressive neurological disorders. *Dysphagia*, *30*(1), 27-46.

Published abstracts

Keage, M. J., Corben, L., Delatycki, M., & Vogel, A. P. (2013). Swallowing function in people with Friedreich's ataxia. *Movement Disorders*, *28*, S240-S241.

Presentations relating to thesis content

2017

Keage, M., Delatycki, M., Dyer, J., Corben, L., & Vogel, A. Dysphagia progression in Friedreich ataxia (poster) – Speech Pathology Australia national conference, Sydney, New South Wales (presenter)

2016

Keage, M., Delatycki, M., Corben, L., & Vogel, A. Dysphagia in Friedreich ataxia (oral presentation) – The University of Melbourne Symposium on progressive neurological disorders of communication and swallowing, Melbourne, Victoria (presenter)

Keage, M., Delatycki, M., Gupta, I., Corben, L., & Vogel, A. (2016). 'Dysphagia in Friedreich Ataxia' (poster) – Speech Pathology Australia National Conference, Perth, Western Australia, Australia (presenter).

2015

Keage, M., Delatycki, M., Corben, L., & Vogel, A. 'Dysphagia in Friedreich ataxia' (poster) – Dysphagia Research Society Annual Meeting, Chicago, Illinois, USA (presenter).

Keage, M., Delatycki, M., Corben, L., & Vogel, A. 'Dysphagia in Friedreich ataxia' (poster) – International Ataxia Conference, Windsor, UK.

Keage, M., Delatycki, M., Corben, L., & Vogel, A. 'Dysphagia in Friedreich ataxia' (oral presentation) – Speech Pathology Australia Dysphagia Interest Group (presenter).

Keage, M., Delatycki, MB., Gupta, I., Corben, LA., Vogel, AP. 'Dysphagia in Friedreich ataxia' (oral presentation) – University of Melbourne School of Health Sciences Research Colloquium, Melbourne, Victoria, Australia (presenter)

Keage, M., Delatycki, MB., Gupta, I., Corben, LA., Vogel, AP. 'Dysphagia in Friedreich ataxia' (oral presentation) – Department of Audiology and Speech Pathology - Thesis Completion Seminar (presenter)

Keage, M., Delatycki, MB., Gupta, I., Corben, LA., Vogel, AP. 'Dysphagia in Friedreich ataxia' (poster) – The Univeristy of Melbourne, Faculty of Medicine, Dentistry and Health Sciences Early Career Researchers Network Symposium (presenter)

2014

Keage, M., Delatycki, M., Corben, L., & Vogel, A. 'Dysphagia in Friedreich ataxia' (oral presentation) – Friedreich Ataxia Research Association, Melbourne, Victoria, Australia (presenter).

Keage, M., Delatycki, M., Corben, L., & Vogel, A. 'Swallowing difficulties in Friedreich ataxia' (oral presentation) - University of Melbourne School of Health Sciences Research Colloquium, Melbourne, Victoria, Australia (presenter).

2013

Vogel, AP., **Keage, MJ**., Schalling, E., Folker, J., & Johansson, K. 'Treatment for dysphagia (swallowing difficulties) in hereditary ataxia syndromes' (oral presentation) – Speech Pathology Australia National Conference, Gold Coast, Queensland, Australia (presenter).

Keage, M., Delatycki, M., Corben, L., & Vogel, A. 'Identification of oropharyngeal dysphagia in progressive neurological disorders: A review of self-reported assessment tools' (poster presentation) – Speech Pathology Australia National Conference, Gold Coast, Queensland, Australia (presenter).

Keage, M., Delatycki, M., Corben, L., & Vogel, A. ‘Swallowing difficulties in people with Friedriech ataxia’ (oral presentation) – Friedreich Ataxia Research Association Scientific Conference, Melbourne, Victoria, Australia (presenter).

Outline of Thesis

Very little is known of the nature and severity of swallowing impairment (dysphagia) in individuals with Friedreich ataxia (FRDA); the most common of the hereditary ataxia syndromes affecting 1 in every 20,000 to 40,000 individuals in European populations. FRDA is a debilitating condition characterised by degeneration of the central and peripheral nervous systems, along with impairment of the skeletal, endocrine, and cardiac systems. FRDA is associated with significant mortality and premature mortality, with death usually occurring in the third or fourth decades of life.

Dysphagia (swallowing impairment) is associated with significant morbidity and can be fatal in severe cases. Individuals with dysphagia are at a high risk of malnutrition, dehydration, and pneumonia secondary to aspiration (matter entering the lungs). Dysphagia affects quality of life (QOL) by taking away some or all of the pleasurable aspects of eating and drinking. Dysphagia is known to exist in individuals with FRDA however the underlying mechanisms are poorly understood.

The overarching aim of this thesis is to determine the impact and nature of dysphagia and frequency of aspiration in individuals with FRDA, and determine the relationship between clinical markers of FRDA and swallowing impairment. Predictors of aspiration in the FRDA population are also investigated.

The thesis is separated into two main parts. The first considered the literature pertaining to FRDA (Chapter 1), swallowing and dysphagia (0), and assessment of dysphagia in progressive neurological disorders (Chapter 3). Chapter 3 also reports a comprehensive discussion of subjective assessments of swallowing appropriate for use in individuals with neurodegenerative disease which has since been published in an academic journal (*Dysphagia*). The second part consists of four studies investigating dysphagia in individuals with FRDA. Swallowing function was considered using a QOL measure, a standardised assessment of oromotor function, and videofluoroscopy (VFSS) (which is considered current best practice). The clinical course of dysphagia in FRDA is also explored on a smaller subset of individuals who underwent longitudinal analysis.

PART A:

Chapter 1

Friedreich Ataxia

Chapter 1 provides a review of FRDA, including disease aetiology, pathology and symptomology. It is important to have a sound understanding of the disease and its associated symptoms when considering dysphagia in this population. In this chapter, clinical measurement scales reported in the literature for FRDA are discussed and the importance of such tools is highlighted in measuring the progression of FRDA.

0

Swallowing and dysphagia

0 describes the phases of normal adult swallowing. Swallowing is described with reference to swallowing-related anatomy and neurogenic dysphagia. Dysphagia in the hereditary ataxia syndromes is broadly covered, and the limited empirical data on treatment is highlighted as a major clinical issue. A clear understanding of swallowing and dysphagia is an important precursor for a detailed investigation into FRDA-related swallowing impairment.

Chapter 3

Dysphagia assessment in progressive neurological disorders

Chapter 3 discusses current clinical standards for swallowing assessment in neurodegenerative disease. Swallowing screening and assessment takes many forms, including clinical bedside examination, subjective swallowing assessments and instrumental analysis. Each approach is reviewed, including detailed review of subjective swallowing questionnaires to identify which tool is best suited for describing dysphagia in individuals with progressive neurological disease.

PART B: Studies 1, 2, 3 and 4

Chapter 4

Study 1 - Swallowing-related quality of life in individuals with Friedreich ataxia

Chapter 4 describes a detailed investigation of the impact of dysphagia on individuals with FRDA. The chapter includes a review of the psychosocial implications of swallowing impairment and a sound rationale as to why this is an important area of research in FRDA-affected individuals. Individuals with FRDA were invited to complete a swallowing quality

of life questionnaire and results were compared to a sample of healthy age matched controls. The results obtained in this study highlight the consequences of FRDA-related dysphagia, and necessitate the need for further research in this area. The data from this research are examined in Study 3 - A videofluoroscopic analysis of swallowing in individuals with FRDA to determine predictors of aspiration in FRDA.

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Study 2 - Clinical bedside examination of oromotor function and swallowing in FRDA using a standardised assessment

In this chapter, individuals with FRDA identified as at risk of dysphagia are examined using a standardised measure of oromotor function; the Frenchay Dysarthria Assessment (2nd edition) (FDA-2). A comprehensive oromotor exam is an important step in the dysphagia assessment process. Previous studies have shown that the FDA-2 is a suitable assessment for use in the FRDA population and correlates with measurements of ataxia severity (Eigentler et al., 2012). The aims of this study are to characterise FRDA-related oromotor dysfunction, as well as establish the relationships (if any) between oromotor dysfunction and FRDA clinical parameters. The results of this study are further examined in Study 3 - A videofluoroscopic analysis of swallowing in individuals with FRDA, where the predictive qualities of aspiration (matter entering the lungs) in FRDA is explored.

Chapter 6

Study 3 - A videofluoroscopic analysis of swallowing in individuals with FRDA

This cross-sectional study is the first to comprehensively characterise dysphagia in FRDA and document the frequency of concomitant penetration and aspiration. Swallowing function was evaluated using the current clinical gold standard – videofluoroscopic study of swallowing (VFSS). Furthermore, correlations were made between VFSS results and FRDA clinical parameters to investigate the relationship between dysphagia and disease severity, duration, and genetic aetiology. The results of Study 1 - Swallowing-related quality of life in individuals with Friedreich ataxia and Study 2 – Clinical bedside examination of oromotor function and swallowing in FRDA using a standardised assessment are correlated with VFSS data and predictors of significant airway compromise were considered using logistic regression analysis.

Chapter 7

Study 4 - A longitudinal analysis of swallowing in individuals with FRDA

This study documents the clinical course of dysphagia in individuals with FRDA. A cohort of 26 of the original 60 participants underwent repeat assessment approximately 12 months following initial assessment. The methodology from Study 1 - Swallowing-related quality of life in individuals with Friedreich ataxia, Study 2 – Clinical bedside examination of oromotor function and swallowing in FRDA using a standardised assessment and Study 3 - A videofluoroscopic analysis of swallowing in individuals with FRDA were replicated This study is important given dysphagia is known to worsen over time in other neurodegenerative conditions.

PART C:

Chapter 8

Summary, limitations and future directions

This chapter recapitulates the major findings from the four studies presented in this thesis, and provides an overview related to each of the study hypotheses. Findings are reported to provide a concise overview of swallowing function and the clinical course of dysphagia in individuals with FRDA. The limitations of this doctoral research are discussed, as are the clinical implications of the findings and directions for future work in the field.

Chapter 1 Friedreich Ataxia

1.1 Introduction

Chapter 1 provides a comprehensive description of Friedreich ataxia (FRDA), including aetiology, pathology and symptomology. It covers the framework and biological basis for determining the impact of swallowing impairment of individuals with FRDA.

1.2 Friedreich ataxia

Friedreich ataxia (FRDA) is an autosomal recessive disease affecting one in every 20,000 to 40,000 individuals in European populations (Delatycki, Williamson, & Forrest, 200, Schulz et al., 2009; Vankan, 2013). FRDA is the most prevalent of the hereditary ataxia syndromes (HASs); a highly heterogeneous group of disorders associated with progressive incoordination of gait, poor coordination of upper limbs, speech and visual disturbances, among other symptoms (Bird, 2016). FRDA was first described by German physician and pathologist Nikolaus Friedreich between 1863 and 1877 in a series of five papers (Friedreich 1863, 1863a, 1863b, 1876 and 1877). Friedreich noted a distinct cluster of symptoms including ataxia, dysarthria, sensory loss, muscle weakness, scoliosis, foot deformity, cardiac issues, and absent deep tendon reflexes (Delatycki, Williamson, & Forrest, 2000). The mutated gene which causes FRDA was discovered in 1996 by Campuzano and colleagues, and subsequently various phenotypes of FRDA have been identified (to be discussed in 1.5 Phenotype-genotype correlations).

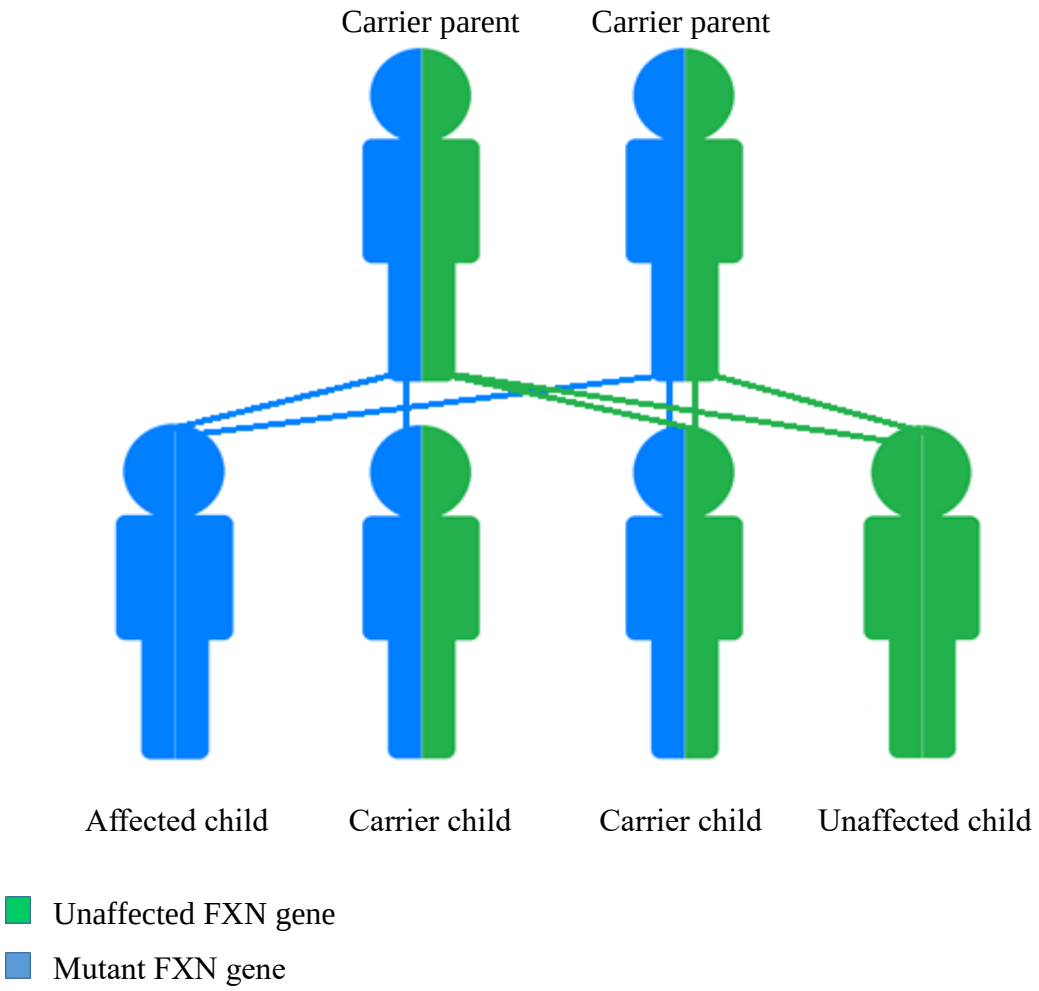
1.3 Molecular basis of FRDA

In 96% of cases FRDA arises due to homozygosity for the GAA trinucleotide repeat expansion in intron 1 of the *FXN* gene. The remaining 4% of cases arise due to compound heterozygosity for the GAA expansion and point mutation or deletion (Delatycki & Corben, 2012). The *FXN* gene is responsible for encoding frataxin which is a protein localised in the mitochondria of the body's cells (Leidgens, De Smet, & Foury, 2010; Pandolfo & Montermini, 1998; Santos et al., 2010). The exact function of frataxin is unknown however it has been implicated in the process of iron-binding and the formation of iron-sulphur clusters which are a critical components of the cellular respiratory chain (the electron-transport chain) (Klockgether & Paulson, 2011). Frataxin is most highly expressed in tissues with a high metabolic rate, such as neural tissue, cardiac muscle, liver, skeletal muscle, and pancreas (Durr et al., 1996). Iron-sulphur clusters are formed due to the interaction of frataxin with the Isu1 protein which acts as a scaffold on which iron-sulphur clusters are built (Gerber,

Mühlenhoff, & Lill, 2003). This interaction has been shown to occur at the beta-sheet component of the frataxin protein (Leidgens et al., 2010).

Alleles ranging from 56 to 1300 GAA triplets in length have been identified in people with FRDA, whereas unaffected individuals present with between six and 36 GAA triplets (Pandolfo & Montermini, 1998). Durr and colleagues (1996) have reported an upper limit of 1700 GAA triplets in length, however these results have not been replicated in other studies (Delatycki et al., 2000). The size of the smaller allele (GAA1) is inversely correlated with the amount of residual frataxin present in lymphoblast cells (Cossee et al., 1997). Most cases of FRDA are linked to chromosome 9 markers *D9S5* and *D9S15*, indicating strong gene locus homogeneity (Chamberlain et al., 1988; Fujita et al., 1989). However in some rare cases of typical FRDA there is no mutation in this gene, suggesting the existence of a second FRDA locus (Delatycki et al., 2000).

Figure 1-1 FRDA mode of inheritance



1.4 Variants of FRDA

Up to 25% of individuals who are homozygous for the GAA triplet repeat expansion in *FXN* present with an atypical FRDA phenotype (Bidichandani, Garcia, Patel, & Dimachkie, 2000) including Late Onset Friedreich Ataxia (LOFA), very late onset FRDA (VLOFA), and Friedreich Ataxia with Retained Lower Limb Tendon Reflexes (FARR) (Bidichandani et al., 2000; Durr et al., 1996). Clinically these variants are considered a reflection of the FRDA severity and symptom spectrum, rather than separate conditions, especially as the GAA1 allele length has been shown to account for some of the differences observed (Campuzano et al., 1997).

LOFA occurs in approximately 14% of cases and is characterised by symptom onset after 25 years of age (Bhidayasiri, Perlman, Pulst, & Geschwind, 2005). In VLOFA symptoms appear after the age of 40 years (Berciano et al., 2005). Individuals with FARR present with brisk lower limb reflexes, notably knee jerks, and is found in approximately 10% (Palau et al., 1995) (Coppola et al., 1999) of affected individuals.

Compared to typical FRDA, individuals with LOFA have been shown to have a significantly smaller GAA repeat size on both alleles and less severe functional disability (Lecocq et al., 2015). Furthermore, clinical manifestations including dysarthria, abolished tendon-reflexes, extensor plantar reflexes, weakness, atrophy, ganglionopathy, cerebellar atrophy, scoliosis, and cardiomyopathy are less prevalent in in LOFA and VLOFA when compared to typical FRDA (Bhidayasiri et al., 2005; Lecocq et al., 2015).

Acadian FRDA

Acadian FRDA is a milder, more slowly progressing variant of FRDA specific to the Acadian population in New Brunswick, Canada (Richter et al., 1996). These individuals present with a GAA1 repeat length representative of typical FRDA, however symptoms tend to emerge later in life and the disease progression is slower. Cardiomyopathy is also less severe in this population (Montermini et al., 1997).

1.5 Phenotype-genotype correlations

The variable nature and progression of FRDA can be partially explained by the repeat size on the smaller GAA allele (GAA1) which inversely correlates with frataxin expression (Bidichandani, Ashizawa, & Patel, 1998). Symptom onset, severity, and progression of the disease have been shown to inversely correlate with GAA1 repeat size (Pandolfo & Montermini, 1998). Earlier onset of disease and the time until confinement to a wheelchair is

associated with larger GAA1 expansions (Durr et al., 1996), as is the presence of diabetes and cardiomyopathy (Filla et al., 1996). The length of the GAA2 repeat does not contribute to clinical phenotype to the same extent as GAA1 (Delatycki et al., 1999; Durr et al., 1996), however has been implicated in LOFA. Individuals with LOFA have significantly shorter GAA expansions on both alleles when compared to more typical onset FRDA (Koeppen, 2011).

1.6 Incidence

One in every 29,000 Caucasian individuals is estimated to be affected by FRDA, and 1 in every 85 individuals is estimated to carry the gene (Cossee et al., 1997). A review of epidemiological studies in FRDA reported the prevalence gradient of FRDA from western to Eastern Europe, with the highest levels observed in northern Spain, the south of France, and Ireland. The lowest levels were recorded in Scandinavia and Russia (Vankan, 2013). FRDA rarely affects individuals of south-east Asian or African decent (Delatycki & Corben, 2012).

1.7 Pathology

The pathological phenotype of FRDA is variable and includes the heart, pancreas, skeleton, and the central and peripheral nervous systems. In the nervous systems the primary site of degeneration is the dentate nucleus of the cerebellum, as well as the dorsal root ganglia, the posterior columns of the spinal cord, the corticospinal tracts, and the heart (Delatycki et al., 2000). The dorsal root ganglia in individuals with FRDA (including those with LOFA) are characteristically smaller in size and have residual nodules of Nageotte (Koeppen, 2011; Koeppen et al., 2009). Sensory peripheral neuropathy is almost universal in individuals with FRDA and is most severe in the lower limbs (Koeppen & Mazurkiewicz, 2013). Myelin degeneration in the corticospinal tracts has been identified in autopsy studies (Koeppen, 2011) along with thinning of the distal portal of the pyramidal tracts. This pattern of degeneration indicates a dying back process from the periphery (Delatycki et al., 2000). Atrophy of the neurons in the dorsal nuclei of Clarke is also a feature of FRDA, as well as fibre loss in the spinocerebellar and corticobulbar tracts (Koeppen, 2011). The most prevalent cardiac pathology seen in FRDA is cardiomyopathy apparent as hypertrophy and may eventually lead to heart failure (Weidemann et al., 2013) (to be discussed later in this chapter in 1.8.2.1 Cardiomyopathy).

1.8 Clinical manifestations of FRDA

1.8.1 Neurological

1.8.1.1 Ataxia

Progressive ataxia is a hallmark feature of FRDA (Harding, 1981) and arises in part due to disturbance of the proprioceptive systems, primarily the deep nuclei of the cerebellum, corticospinal tracts, and the sensory systems (visual and vestibular), as well as motor disturbance. Axonal degeneration occurs in the corticospinal tract of the spinal cord, resulting in the absent lower limb reflexes and upgoing plantar responses (Pandolfo, 2009). FRDA-related ataxia is both afferent (due to proprioceptive disturbance) and efferent (due to cerebellar degeneration) and imposes significant functional implications. Limb function and control is characterised by dysmetria, dysdiadochokinesia, and intention tremor (Koeppen, 2011; Pandolfo, 2003). Mobility is affected by balance and gait disturbances (Pandolfo, 2009), whilst vision is affected by instability of fixation and square wave jerks (Fahey et al., 2008; Pandolfo, 2009). Speech becomes dysarthric (Folker et al., 2010) and swallowing function can deteriorate (Vogel, Brown, Folker, Corben, & Delatycki, 2014). These manifestations present a major restriction in terms of ability to complete activities of daily living (ADLs) (Pandolfo, 2009).

1.8.1.2 Weakness

Neuropathological studies of FRDA have revealed degeneration of the pyramidal tracts, with the distal portion being more severely affected indicating dying back pathology (Koeppen, 2011). In the corticospinal tracts there is prominent myelin and axon loss which may be visible to the naked eye (Koeppen, 2011). This neuropathology manifests in slowing of central motor conduction time and reduction in motor evoked potentials, which have both been shown to correlate with disease duration (Cruz-Martínez & Palau, 1997; Santoro et al., 2000). Magnetic resonance spectroscopy studies have shown reduced mitochondrial adenosine triphosphate (ATP; an enzyme responsible for transporting energy within the cell) expression in individuals with FRDA (Lodi et al., 1999; Lodi et al., 2001). Reduced ATP production is reported to correlate with GAA1 repeat length (Lodi et al., 2001; Santoro et al., 2000). Santoro and colleagues (2000) reported slowing of the central motor conduction time and reduction in the intensity of motor evoked potential in individuals with FRDA, with strong correlations observed with disease duration. Iron deficiency is thought to exacerbate fatigue and weakness in FRDA (Li, Besse, Ha, Kovtunovych, & Rouault, 2008).

1.8.1.3 Spasticity

Spasticity arises due to lesions of the pyramidal tract and is present in approximately 15% of individuals with atypical FRDA (Geoffroy et al., 1976). The presence of spasticity is compounded by co-activation of the agonist-antagonist muscles, loss of selective motor control, and impaired sequencing and timing between muscles. These factors results in restricted movement, stiffness, spasms and pain (Burtner, Woollacott, & Qualls, 1999; W Ilg et al., 2009). Spasticity affects many parts of the body and contributes to some of the symptoms experienced by individuals with FRDA, including restricted upper and lower limb movement, impaired manual dexterity, and speech and voice disturbance. Isolating the impact of spasticity on function in individuals with FRDA is problematic given coexisting degeneration of the dorsal root ganglia and the cerebellum (Corben, Lynch, Pandolfo, Schulz, & Delatycki, 2014).

1.8.1.4 Sensory disturbances

Sensory disturbances seen in individuals with FRDA are reflective of degeneration of the large sensory neurons in the dorsal root ganglia (DRG). FRDA manifests in a reduction in the size of the DRG, as well as a loss of larger myelinated fibres (Morral, Davis, Qian, Gelman, & Koeppen, 2010). Dürr and colleagues (1996) reported up to 98% of individuals with FRDA present with axonal neuropathy, which directly affects sensation. In a retrospective study of 56 individuals with FRDA, Santoro and colleagues (1999) reported a correlation between sensory neuropathy (including sensory action potential amplitude and percentage of myelinated fibres) and GAA1 repeat size. Degeneration of the dorsal columns of the spinal cord results in decreased vibration sensation and proprioception (Pandolfo & Manto, 2013). Additionally, awareness of light touch and temperature can decrease as the disease progresses (Pandolfo, 2009). Autonomic disturbances can also arise from FRDA, and manifest in cold and cyanosed distal lower limbs, usually seen in the later stages of the disease (Pandolfo, 2009).

1.8.1.5 Restless legs

Restless leg syndrome is a neurological motor disorder characterised by an irresistible urge to move the legs and associated with unpleasant sensation in the legs (Ekbom & Ulfberg, 2009). It is present in 2% to 15% of individuals with FRDA (Frauscher et al., 2011; Matthis Synofzik, Godau, Lindig, Schöls, & Berg, 2011). The exact aetiology of restless legs syndrome is unclear (Hening, Allen, Washburn, Lesage, & Earley, 2009).

1.8.1.6 Dysarthria

Speech impairment (dysarthria) is a hallmark feature of FRDA (Pandolfo, 2009) affecting between 91% (Durr et al., 1996) to 100% (Folker et al., 2010a) of individuals. FRDA-related dysarthria is characterised by reduced rate of speech, vocal instability, mixed nasal resonance, and imprecise consonant production (Folker et al., 2010a; Poole et al., 2014). This, along with other changes impacting on communication such as difficulties in auditory processing (Polverino et al., 2012), may impact on the ability to effectively communicate with others (Corben et al., 2014).

Three dysarthria profiles exist in FRDA (Folker et al., 2010a). Approximately a third of individuals with FRDA present with reduced speech intelligibility due to mild impairment in multiple speech domains, including consonant precision, reduced pitch variation, loudness, phrase length, breath support for speech and hypernasality. The remaining two subgroups reflect more severe dysarthria across all of the defined domains. Subgroup 2 presents with features consistent with velopharyngeal incompetence, including reduced pitch variation, phrase length, and increased hypernasality. Subgroup 3 features increased vocal strain, reflective of laryngeal dysfunction (Folker et al., 2010a).

Folker and colleagues (2012) further characterised FRDA-related dysarthria using instrumental analysis to measure respiratory, laryngeal, velopharyngeal and articulatory function. Reduced articulation rate and reduced breath support were noted in a series of seven case studies. Measures of nasality and phonatory dysfunction were required to distinguish between some cases, providing further evidence for the mixed neuropathy leading to speech impairment in individuals with FRDA (Folker et al., 2012). A subsequent study by Poole and colleagues (2014) demonstrated a consistent finding of disturbed nasality in dysarthric individuals with FRDA. In this study of 37 individuals with FRDA, 73% presented with hypernasality on perceptual assessment, whilst 18.5% participants in this study presented with hyponasality. Acoustic analysis of individuals with FRDA and healthy controls found greater nasality in the FRDA group ($p < 0.05$) suggesting significant velopharyngeal dysfunction associated with FRDA (Poole et al., 2014).

FRDA-related dysarthria arises due to disturbed temporal rather than spatial execution. Folker and colleagues (2010b) investigated lingual kinematics in a group of dysarthric individuals with FRDA using electromagnetic articulography (EMA) to evaluate lingual-to-palate contact across sentence utterances compared to healthy controls. The individuals with

FRDA produced longer movement durations and movement distances, as well as slower maximum velocities during the approach phase of consonant production (movement of the tongue up to the palate). The study provided evidence for the articulatory impairment associated with FRDA manifesting as a temporal rather than a spatial disturbance. Similar results have been demonstrated in the production of lingual sounds (Folker, Murdoch, Cahill, Delatycki, Corben, & Vogel, 2011).

Dysarthria is related to disease duration and severity, and the length of the larger GAA repeat (GAA2) (Folker at al., 2010a). Brendal and colleagues (2015) profiled the severity and characteristics of dysarthria in 20 individuals with FRDA using a battery of speech tasks and two widely used paraspeech tasks (oral diadochokinesis and sustained vowel production). These data were correlated with measures of ataxia severity to determine the relationship between dysarthria and body ataxia however no straightforward relationship was detected. These results suggest that speech is differentially susceptible to FRDA pathology when compared to limb and trunk motor functions (Brendel et al., 2015).

1.8.1.7 Dysphagia

Swallowing impairment (dysphagia) is common in FRDA with symptoms including coughing and choking on liquids and solids (strongly suggestive of aspiration, or matter entering the lungs when swallowing) and nasal regurgitation (Vogel et al., 2014). Data on the nature and progression of dysphagia in people with FRDA is extremely limited. No longitudinal studies exist documenting the onset, nature, progression or characteristics of the swallowing deficits in this population. An inverse relationship with GAA1 repeat length has been found for onset of dysphagia (Schöls et al., 1997), however the link between dysphagia severity and size of the GAA repeat has not been investigated. Anecdotal reports suggest individuals with FRDA often choke, require modified foods or alternative feeding (such as nasogastric feeding) as the disease progresses, implying a relationships between disease progression and dysphagia severity (Pandolfo, 2009).

Vogel and colleagues (2014) present the first detailed study of dysphagia in FRDA and reported dysphagia in 35/36 (97.22%) participants on at least one of four non-instrumental measures of swallowing, including a clinical bedside examination (CBE) and oral motor examination, the Royal Brisbane Hospital Outcome Measure for Swallowing (RBHOMS) (Ward & Conroy, 1999), and the Australian Therapy Outcome Measure for Speech and Swallowing (AusTOMS) (Perry & Skeat, 2004). The RBHOMS describes the presence of

dysphagia as well as changes to swallowing function over time. Ratings on the RBHOMS indicate level of independence and safety of eating in the context of diet modification and safe-swallowing strategy use (Ward & Conroy, 1999). The AusTOMS for Speech Pathology considers dysphagia according to impairment, activity, participation and well-being outlined in the World Health Organization's (WHO) International Classification of Functioning, Disability and Health (ICF) (Perry & Skeat, 2004). Vogel and colleagues (2014) reported 33/36 participants (91.76%) with FRDA presented with clinical signs of dysphagia in the CBE. Dysphagia was shown to impose functional limitations and affect overall quality of life (QOL) in individuals with FRDA. A significant positive correlation was found between the severity of impairment, activity, participation and distress/well-being components of the AusTOMS, suggesting a link between swallowing deterioration and reduced QOL. A significant relationship was also reported between activity restriction related to swallowing impairment and disease duration. No significant correlations were found between dysphagia severity and GAA repeat length, age of onset or disease severity (Vogel et al., 2014).

1.8.1.8 Vision

Vision disturbance is common in FRDA and arises due to several neuropathological processes (Delatycki & Corben, 2012; Fielding et al., 2010). Fahey and colleagues (2008) reported widespread dysfunction of the ocular motor system in individuals with FRDA including square wave jerks, fixation abnormalities and prolonged saccadic latency with hypometria and hypermetria. A relationship has been reported between mean saccadic latency and disease severity (as measured by the Friedreich Ataxia Rating Scale (FARS) score), suggesting saccadic impairment increases in line with disease severity (Fahey et al., 2008). Optic atrophy is another feature of FRDA (Fortuna et al., 2009) and manifests in reduced visual acuity that is severe in about 10% (Lynch, Farmer, Rochestie, & Balcer, 2002).

Data from optical coherence tomography and contrast letter acuity testing have revealed significant relationships between disease clinical parameters and visual function (Noval, Contreras, Sanz-Gallego, Manrique, & Arpa, 2011; Seyer et al., 2013). High and low contact letter acuity is shown to be predicted by age, GAA repeat length, and disease severity. Retinal nerve fibre thickness was also reduced in individuals with FRDA and correlated with disease severity (as measured by the FARS) (Seyer et al., 2013).

1.8.1.9 Bladder and bowel function

Bladder dysfunction affects 23% to 41% of individuals with FRDA (Delatycki et al., 1999; Durr et al., 1996) and is characterised by bladder overactivity (with urgency being the most frequent symptom reported) (Vezina, Bouchard, & Bouchard, 1982) and limited bladder capacity (Nardulli et al., 1991; Vezina et al., 1982), likely secondary to degeneration of the pyramidal tracts (Schulz et al., 2009). Bowel dysfunction (incontinence and constipation) is reported in FRDA (Chung & Emmanuel, 2006), however research pertaining to incidence and severity is lacking. The aetiology of bowel dysfunction in FRDA is unclear, however it is thought to arise from autonomic and pelvic nerve dysfunction manifesting in distorted motor function and disturbed anorectal sensation and reflexes (Craggs, Balasubramaniam, Chung, & Emmanuel, 2006).

1.8.1.10 Audiological function

Abnormalities in the auditory pathway and disturbances in functional hearing ability reported in FRDA (Lynch et al., 2002), impacting on speech perception and ability to communicate with others (Rance et al., 2008). Rance and colleagues (2008) profiled the auditory function of individuals with FRDA and revealed clear electrophysiological evidence of auditory pathway disorder in 3/10 (30%) of the participants, and abnormal speech perception in 9/10 (90%). These results demonstrate that while detection of sounds may be within normal limits in people with FRDA, accurate sound perception can be disrupted by auditory nerve dysfunction (Rance et al., 2008).

In a follow up study, Rance and colleagues (2012) studied 19 school-aged individuals with FRDA and found that sound detection in a quiet environment was within normal limits, however auditory temporal processing and speech understanding were severely impaired particularly in the presence of background noise when compared to healthy controls. The children with FRDA were able to interpret less than 40% of the information presented compared with the controls. Functionally, this impaired ability to access auditory information has the potential to impact upon the child's performance in the classroom and interaction with peers. (Rance, Corben, & Delatycki, 2012).

1.8.1.11 Cognition

The cognitive deficits associated with FRDA are heterogeneous in nature and archetypally do not restrict participation in employment or personal relationships (Corben, 2014). A range of cognitive deficits have been reported in FRDA, including reduced flexibility of thought,

reduced visuospatial reasoning, slowed information processing, attention deficits, and reduced working memory, and reduced learning capacity (Corben et al., 2011; Fielding et al., 2010; Hocking et al., 2014; Mantovan et al., 2006; Nieto et al., 2012). Cognitive dysfunction is reported to relate to GAA repeat length, age at disease onset, and disease severity (Nachbauer et al., 2014). FRDA also affects motor planning (Corben et al., 2011). Individuals with FRDA are reported to have reduced capacity to generate a motor response to incongruent stimuli (Corben et al., 2011), and to accommodate changes in moving to targets differing in size and distance apart (Corben et al., 2010).

Individuals with FRDA present with deficits in brain activations during working memory and executive functioning tasks when compared to healthy controls (Harding et al., 2016). Using fMRI, Harding and colleagues (2016) revealed disturbed activations in the lateral cerebellar hemispheres and the prefrontal cortex (including regions of the anterior insular and rostrolateral prefrontal cortices) in individuals with FRDA compared to healthy controls during a working memory task. Connectivity between these regions was always impaired. Correlations between behavioural performance on the cognitive task and cerebral activations were observed in the healthy controls in this study, but not in the FRDA group (Harding et al., 2016).

1.8.2 Non-neurological manifestations

1.8.2.1 Cardiomyopathy

Cardiac disease is the leading cause of death in FRDA (Tsou et al., 2011). Cardiac symptoms related to FRDA commonly arise in the first or second decades of life (Harding, 1981), and typically before the age of 40 years (Weidemann et al., 2012; Weidemann et al., 2013). In rare cases, cardiomyopathy can be the heralding symptom of the disease (Quercia et al 2011).

Consensus is yet to be reached on the correct terminology to accurately describe involvement in FRDA (Peverill, Lynch & Payne, in Corben et al., 2014). Hausse and colleagues (2002) describe progressive hypertrophic cardiomyopathy related to FRDA, however Payne and colleagues (2012) argue this leads to the cardiomyopathy associated with FRDA being easily confused with that seen in autosomal dominant hypertrophic cardiomyopathies, which arise from different aetiology. Additionally, the term ‘hypertrophic’ infers an increased left ventricular mass, however in FRDA there is generally an increase in relative wall thickness in the absence of an increase in left ventricular mass (Mottram et al., 2011; Regner et al., 2012). Systolic function is generally preserved in people with FRDA. Individuals with end-stage

cardiomyopathy present with a reduced ejection fraction (a measurement of blood volume in the left ventricle that is pumped out with each ventricular contraction) with global hypokinesia and dilation of the left ventricle (Regner et al., 2012; Weidemann et al., 2012; Weidemann et al., 2013). Myocardial fibrosis has also been shown to develop in the later stages of FRDA, further impacting on cardiac function (Raman et al., 2010).

Studies using cardiac magnetic resonance imaging (cMRI) show a positive correlation between left ventricular mass and the length of GAA1 and age at disease onset (Weidemann et al., 2013). Left ventricular mass was also shown to decrease with disease duration, suggesting a correlation between cardiac thinning with advancing disease (Rajagopalan et al., 2010).

Despite the left ventricular hypertrophy commonly seen in FRDA, QRS duration is normal on electrocardiographic studies, which is in contrast to other hypertrophic cardiomyopathies (Weidemann et al., 2012). Left ventricular hypertrophy is reflected by the finding of high S-wave in V1 and V2, and an increased R wave in V5 and V6 (Dutka, Donnelly, Nihoyannopoulos, Oakley, & Nunez, 1999; Weidemann et al., 2012). T wave abnormalities are also frequent in patients with FRDA (Payne & Peverill, 2012).

1.8.2.2 Scoliosis

Scoliosis affects over 60% of individuals with FRDA (Milbrandt, Kunes, & Karol, 2008). Onset generally occurs between the ages of 5 to 20 years (Milbrandt et al., 2008). Progression and severity are variable. Typically if onset is prior to 10 years of age, scoliosis becomes more severe and is faster to progress, resulting in a spinal curve greater than 60 degrees. In cases where onset is later than 10 years of age, progression is slower and the overall severity is less, manifesting in curvature less than 40 degrees (Labelle, Tohme, Duhaime, & Allard, 1986).

The type of spinal deformity seen in individuals with FRDA can manifest as a single thoracic curve or double major curves. Double major curves have been shown to present in 33% of individuals with FRDA, left-sided thoracic curves in 22%, and hyperkyphosis in 24.4% (Milbrandt et al., 2008). It is possible that spasticity is a major contributing factor in the development of scoliosis in people with FRDA, although this hypothesis has not been confirmed (Corben et al., 2014).

1.8.2.3 Diabetes

Diabetes is present in 8% to 32% of individuals with FRDA, with discrepancy likely due to the method of testing and diagnostic criteria (Cnop, Mulder, & Igoillo-Esteve, 2013). The correlation, if any, between diabetes and GAA trinucleotide expansion length remains unclear (Cnop et al., 2013). Cnop and colleagues (2013) did not find a significant relationship between GAA repeat length and the presence of diabetes in a cohort of 51 people with FRDA, however Delatycki and colleagues (1999) reported an inverse relationship between both disease duration and age of onset with the presence of diabetes.

1.9 Life expectancy

FRDA is associated with premature mortality. A study involving 61 participants reported that the mean age at death was 37.5 years, while the median was 30 years (Tsou et al., 2011). The most common cause of death in FRDA is cardiac dysfunction (59%), most frequently from congestive heart failure or arrhythmia. Other causes of death in FRDA include probable cardiac dysfunction (3.3%), non-cardiac issues (27.9%), and unknown causes (9.8%) (Tsou et al., 2011). Pneumonia, a common sequela of dysphagia, accounts for 10% of deaths of individuals with FRDA (Tsou et al., 2011).

1.10 Quality of life

A number of factors affect the QOL of individuals with FRDA and should be at the forefront of clinical decision-making. Individuals with FRDA are at a higher risk of mood disturbance when compared to individuals without FRDA (Flood & Perlman, 1987; Giordani et al., 1989; Wilson et al., 2007), ranging from mild grief-related reactive depression to severe depression (Flood & Perlman, 1987). Higher rates of anxiety, depression, and social isolation have also been documented in individuals with FRDA compared to healthy controls (Giordani et al., 1989).

Wilson and colleagues (2007) and Epstein and colleagues (2008) investigated the impact of FRDA on QOL using a self-completed generic tool: the 36-item Medical Outcomes Study Short Form Health Survey Version 2 (SF-36V2). Whilst not specific to FRDA, the SF-36V2 covers multiple QOL domains and allows for an overall estimate of physical and mental health to be calculated through two subcategories: a physical component, and a mental component. In both studies, the physical and mental components of health-related QOL were reduced in individuals with FRDA. In the study by Wilson and colleagues (2007), even individuals in the early stage of FRDA recorded worse QOL scores. Disease severity and age

of onset showed the strongest correlation with the physical component summary of the SF-36V2. Additionally, results indicated that the later the age of disease onset, the worse the physical QOL scores were. Higher perceived physical QOL was associated with access to social contact and support, and to economic resources. No significant correlation was seen between physical QOL and participant's age, gender, employment status, or education level. In regards to the mental component, disease duration was the only factor with a significant association. The authors found that as the period of time since the onset of FRDA increases, mental health QOL is perceived to be better (Wilson et al., 2007).

In paediatric FRDA cohorts, QOL has been investigated using the Pediatric Quality of Life Inventory (PedsQL) (Brandsema, Stephens, Hartley, & Yoon, 2010; Paulsen, Friedman, Myers, & Lynch, 2010). Both children with FRDA and their parents reported reduced QOL when compared to healthy control groups reported in the literature (Paulsen et al., 2010). These results were supported in a study by Brandsema and colleagues (2010), who reported lower PedsQL scores in a group of seven children with FRDA.

1.11 Treatment

There is no cure for FRDA however advances in the understanding of the pathogenesis of FRDA (including the epigenetic consequences of the expanded GAA repeat to the differences in iron metabolism induced by frataxin deficiency) has led to advancements in the development of potential treatments for the condition (Corben et al., 2014).

1.11.1 Pharmacological treatment

There are varying pharmacological agents being investigated as potential treatments for FRDA with a focus on increasing the cellular frataxin levels (Perlman, 2012). Such treatments include gene and protein replacement, histone deacetylase inhibitors, erythropoietin and erythropoietin mimetics, and other molecules (Pandolfo, 2013).

Some therapeutic approaches aim to compensate for the mitochondrial dysfunction resulting from the deficiencies in the iron-sulphur cluster containing units required in the mitochondrial electron transport. One such approach is the combination of coenzyme Q10 (CoQ10) and Vitamin E, an electron carrier and antioxidant. A study involving 10 individuals with FRDA prescribed daily CoQ10 and Vitamin E over a period of 6 months yielded promising results (Lodi et al., 2001), with participants showing improved cardiac and skeletal bioenergetics (calf muscle energy metabolism) ($p=0.03$ and 0.01 respectively) (Lodi et al., 2001). These improvements were greater in prehypertrophic hearts and in the muscles of

patients with longer GAA repeat length (Lodi et al., 2001). A longitudinal follow up study of 47 months of 77 patients with genetically confirmed FRDA treated with vitamin in coenzyme Q10 also mirrored these results. Therapy resulted in improved mitochondrial energy synthesis and cardiac function and a slowed progression of other clinical features (as measured using ICARS) (Hart et al., 2005).

Idebenone, a short chain benzoquinone related to coenzyme Q10, has been tested in a number of studies (Buyse et al., 2003; Hausse et al., 2002; Mariotti et al., 2003; Pineda et al., 2008; Ribaï et al., 2007; Rustin et al., 1999). A systematic review by Kearney, Orrell Richard, Fahey, and Pandolfo (2012) identified 10 studies of the use of idebenone to treat FRDA, however only one randomised controlled trial (RCT) study met the inclusion criteria for the review. The study of 29 participants with FRDA did not yield any significant change in the International Cooperative Ataxia Rating Scale (ICARS) scale when idebenone was compared with a placebo (Mariotti et al., 2003).

1.11.1 Gene therapy

Gene therapy for FRDA is an emerging area of research (Pandolfo, 2013), focusing on gene altering or heterochromatic formation. Both methods aim to increase FXN expression. Frataxin is small in size and therefore can be easily accommodated in vectors, such as the herpes virus, lentivirus, and adeno-associated virus, all of which have been used in cellular and animal models (Pandolfo, 2013) to re-establish frataxin expression (Hebert & Whittom, 2007). The adeno-associated virus vector expressing human frataxin has been shown to prevent and reverse cardiac disease in a mouse model of FRDA (Perdomini et al., 2014).

Epigenetic therapy is also an emerging area in the treatment of FRDA. A histone deactylase inhibitor (HDACi) has been shown to increase FXN mNRA levels and frataxin in a human neuronal cell model, mice and humans (Soragni et al., 2014).

1.11.2 Cell therapy

Using bone marrow derived cells to correct the cardiac and neurological damage in FRDA is an emerging area of research (Evans-Galea et al., 2014). In mice models, transplanted bone marrow derived cells have been detected in the liver, kidney, spleen, lung, and heart tissue, as well as in the bone marrow, thymus and central nervous system (Corti et al., 2002; Jones et al., 2010; Nygren et al., 2004). An increase in neurotrophic activity and improved neuronal survival following transplant of bone marrow derived mesenchymal stem cells (J. Jones et al., 2010). Human mesenchymal stem cells have been reported to increase frataxin expression in

FRDA fibroblasts (Kemp et al., 2011). Increased frataxin expression and improved resistance to oxidative stress have been reported following culturing of neural crest stem cell-like periodontal ligament cells harvested from individuals with FRDA in adipose stem cell-conditioned media (Jones, Estirado, Redondo, Bueno, & Martínez, 2012). Bone marrow derived cells have been shown to repair infarcted cardiac tissue in mice and prolong survival (Orlic, Kajstura, Chimenti, Bodine, et al., 2001; Orlic, Kajstura, Chimenti, Jakoniuk, et al., 2001).

1.11.4 Non-pharmacological treatment

The clinical manifestations of FRDA reduce capacity to perform activities of daily living (ADLs). Allied health therapies, such as Physiotherapy (PT), Occupational Therapy (OT), and Speech Pathology (SP) are important symptom modifying approaches in FRDA (Fonteyn et al., 2014). A systematic review of therapeutic practices in FRDA found PT was the most extensively evaluated followed by OT and SP (Fonteyn et al., 2014). PT approaches for ataxia include exercises targeting balance, gait, coordination, strength, endurance, and posture. Mobility aids, such a walking canes and walking frames, are also commonly prescribed (Fonteyn et al., 2014). In addition, a combination of PT and OT has shown to be beneficial in treating degenerative ataxia, resulting in an overall improvement in activities of daily living participation (Miyai et al., 2012).

Milne and colleagues (2012) provide the first evidence of the efficacy of non-pharmacological treatment for FRDA. An evaluation of 42 admissions to inpatient rehabilitation where goal-related therapy was prescribed noted an increase in functional measures of performances during rehabilitation, and a continuation of improvement during the period immediately after rehabilitation. These results suggest intensive inpatient rehabilitation can halt or reverse the progressive decline in function by individuals with FRDA (Milne et al., 2012). The use of Exergames (physical video gaming) in the physical rehabilitation of individuals with cerebellar disease is gaining traction (Synofzik & Ilg, 2014). Exergame therapy prescribed for eight weeks (two weeks of intensive training followed by six weeks of at home therapy) resulted in functional improvements, as evidence by an average reduction of two SARA points in a sample of 10 children with progressive ataxia (including 4 with FRDA) (Ilg et al., 2012).

A systematic review of the efficacy of speech therapy in the HASs (including FRDA) found insufficient quality evidence to support one specific treatment method (Vogel, Folker, &

Poole, 2014). In this review 14 trials of dysarthria treatment in hereditary ataxia syndromes were identified. Thirteen of the trials compared a medicine to a placebo and the remaining study compared a mix of physiotherapy and occupational therapy treatment with no treatment. No studies measured the efficacy of traditional speech therapies (Vogel, Folker et al., 2014). The primary management option for FRDA-related dysarthria is behavioural modification (Corben et al., 2014). This approach is impairment-level focussed and incorporates the patient's life-role and wishes for treatment. Behavioural strategies include improving underlying physiological support for speech (by improving trunk stability and breath support, for example), compensatory strategies (segmenting phrases and controlling rate of speech), or using alternative and augmentative means for communication, such as technological devices. Environmental modifications, such as reducing background noise, are also commonplace (Corben et al., 2014). The use of FM-listening devices has been reported to improve speech [perception performance in individuals with FRDA to the level of unaffected individuals (Rance, Corben & Delatycki, 2012) and thus enhances communication.

1.12 Measuring FRDA progression

In the last two decades there has been significant research in the development and use of clinical outcome measures in ataxia syndromes. Such tools are essential for the evaluation of disease progression, therapeutic techniques, and also have important implications for clinical research (Bürk, Schulz, & Schulz, 2013; Paap et al., 2016). Bürk and colleagues (2013) emphasise that rating scales should be easy to use and easily incorporated into clinical practice. Additionally, measurement scales should not be susceptible to external factors, floor and ceiling effects, or fluctuations in presentation over the course of a day, or a few days (Bürk et al., 2013).

Since 1997 to present, three appropriate clinical rating tools have been developed to measure progression in FRDA; the Friedreich Ataxia Rating Scale (FARS) (Subramony et al., 2005) International Ataxia Cooperative Rating Scale (ICARS) (Trouillas et al., 1997), and the Scale for the Assessment and Rating of Ataxia (SARA) (Schmitz-Hübsch et al., 2006). The FARS, ICARS, and SARA all contain measures of motor dysfunction related to cerebellar pathology, including ataxia of gait, stance, and limbs. The ICARS and the FARS also consider further aspects of neurological examination such as speech or vision impairment. The FARS is the only tool developed specific to FRDA and considers limitations of the disease in the context

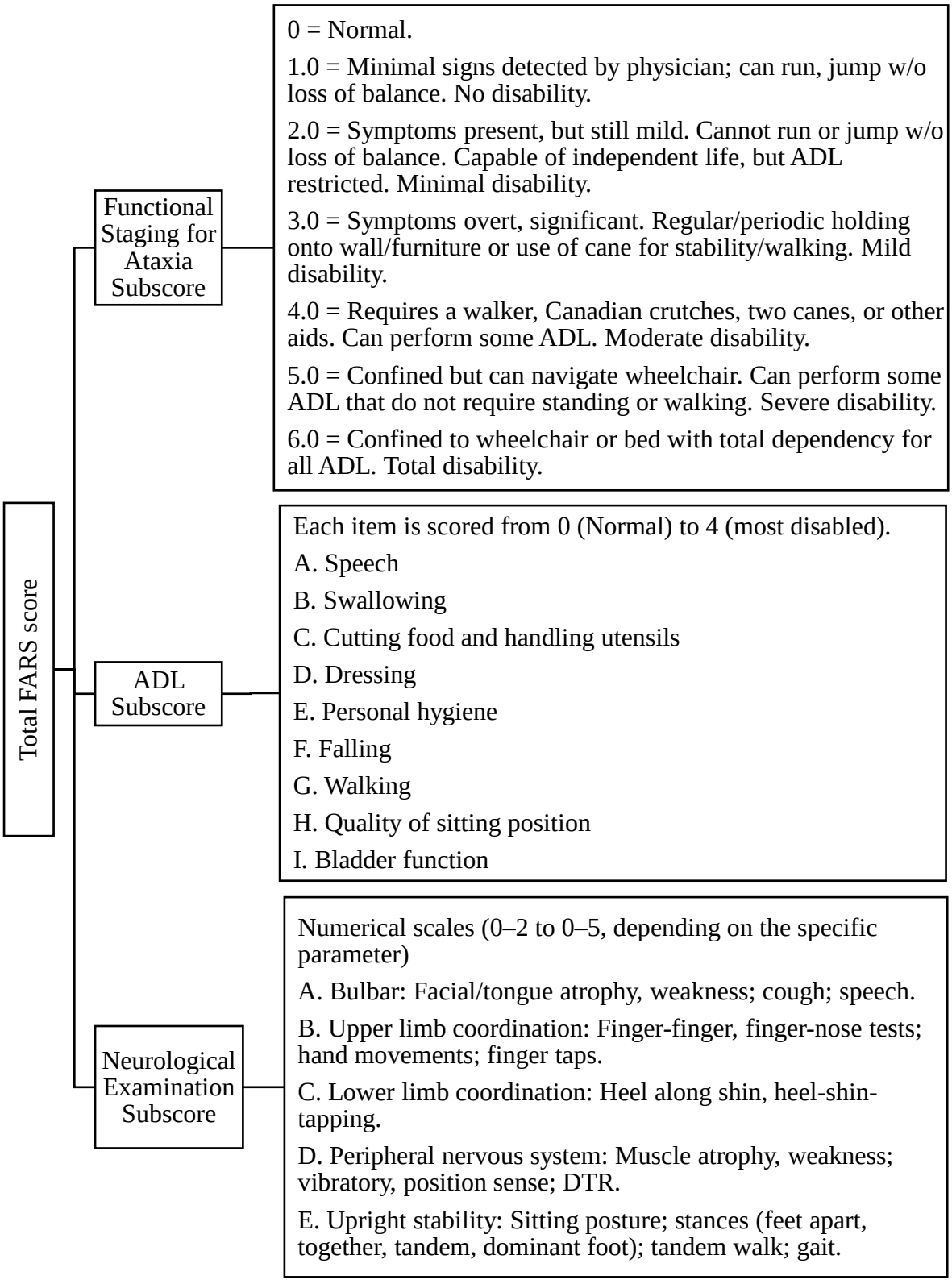
of capacity to complete activities of daily living (Bürk et al., 2013). All three scales have been shown to significantly correlate with each other (Bürk et al., 2009).

1.12.1 Friedreich Ataxia Rating Scale (FARS)

The FARS was developed by Subramony and colleagues (2005) to quantify multiple clinical aspects specific to FRDA. The FARS consists of three subscales: *Ataxia* (6 points), *Activities of Daily Living* (ADL) (36 points), and *Neurological* (117 or 125 points) (Figure 1-2). The FARS is scored from 0-159 or 167, where higher scores equate to greater disease severity (Subramony et al., 2005). The two possible maximum scores arise due to the existence of two versions of the FARS. One version includes two four-point items in the neurological examination subscale, whilst the other version excludes these items (Tai, Yiu, Corben, & Delatycki, 2015). In addition to the areas of assessment outlined above, Subramony and colleagues (2005) applied three supplementary performance measures, including the 'PATA' rate (number of repetitions of the bisyllabic phrase within 10 seconds), the 9-hole peg test (time taken to place and retrieve pegs on a 9 hole pegboard, with an independent rating from the right and left sides) (Grice et al., 2003) and a timed walk of 50 feet.

The FARS was initially evaluated in 14 individuals with FRDA by seven 'raters' (Subramony et al., 2005) and high interrater reliability was established (intraclass coefficient (ICC) > 0.75) for most assessment domains (disease stage, ADL, upper limb and lower limb coordination, stability/gait, sum neurological examination). However, bulbar and peripheral scores were shown to be less reliability (Subramony et al., 2005). The FARS score is not influenced by learning or fatigue (Bürk et al., 2013). The FARS has also been shown to have strong validity by correlations between measures of function in ADLs and mobility with the sum of the neurological assessment components. The FARS has established criterion validity when correlated with the ICARS (described below) and other functional measures (Fahey, Corben, Collins, Churchyard, & Delatycki, 2007), such as the Modified Barthel Index (Shah, Vanclay, & Cooper, 1989) and the Functional Independence Measure (FIM) (Keith, 1987).

Figure 1-2 Summary of the principal components of the FARS (Delatycki, 2009)



1.12.2 International Ataxia Cooperative Rating Scale (ICARS)

The ICARS was the first ataxia-specific rating scale (Paap et al., 2016). It consists of 19 items across four subscales: *Posture and stance* (34 points), *Limb Ataxia* (52 points), *Dysarthria* (8 points), and *Oculomotor Indices* (6 points) (Storey, Tuck, Hester, Hughes, & Churchyard, 2004). These areas of assessment were designed to replicate the functional organisation of the cerebellum (Bürk et al., 2013). The ICARS is scored out of 100, where a higher score indicates more severe symptoms (Trouillas et al., 1997). The ICARS have been appraised for use in multisystem atrophy (MSA), SCA, and FRDA (Schmitz-Hübsch et al., 2006). In a study of 77 individuals with FRDA, the ICARS total score and the sum score all of subscales yielded adequate reliability and validity, ranging from 0.30 to 0.75 (Cano et al., 2005). In the same study, the subscales of the ICARS correlated with age and disease duration in all subscale scores with the exception of the subscale of 'speech disorder'. Metz and colleagues (2013) investigated the ICARS in a sample of 603 individuals with FRDA and found age of onset, disease duration, and GAA repeat length were significant influences on disease progression as measured by the ICARS. The ICARS has been shown to have high inter-rater reliability (Storey et al., 2004), however has been shown to have a significant ceiling effect when used long-term (Folker et al., 2009).

There are two reformed versions of the ICARS: the Brief Ataxia Rating Scale (BARS) and the modified ICARS (MICARS) however both lack further validation (Paap et al., 2016). The BARS was developed for use by movement disorder specialists and neurologists and the MICARS has further items added from the original ICARS format (Storey et al., 2004).

1.12.3 Scale for the Assessment and Rating of Ataxia (SARA)

The SARA was specifically designed to measure symptoms of dominant spinocerebellar ataxia (SCA), and was later validated in the FRDA population by Bürk and colleagues (2009). The SARA is scored between 0 (no ataxia) to 40 (most severe ataxia). The items are divided into eight subtests: *Gait* (8 points), *Stance* (6 points), *Sitting* (4 points), *Speech Disturbance* (6 points), *Finger Chase* (4 points), *Nose-Finger Test* (4 points), *Fast Alternating Hand Movements* (4 points), and *Heel-Shin Slide* (4 points). For measures of limb function an independent rating is made for both sides of the body. The SARA has been shown to correlate with the FARS ($r=0.938$, $p < 0.0001$) (which is the only FRDA specific tool reported in the literature) and has high construct validity when compared to other functional measures, including the ICARS ($r=0.953$, $p < 0.0001$) (Bürk et al., 2009).

1.13 Summary

FRDA is an inherited debilitating condition manifesting in a plethora of symptoms. Dysphagia is prevalent in FRDA and is known to impose significant burden and negatively impact on QOL (Vogel, Brown, Folker, Corben, & Delatycki, 2014). Furthermore, pneumonia (a common sequela of dysphagia) accounts for 10% of deaths in FRDA (Tsou et al., 2011). Despite this, dysphagia in FRDA remains poorly understood.

The present study objective proposes a comprehensive new analysis of dysphagia specific to FRDA, in line with the current clinical standard of swallowing assessment. The study is to better describe and understand swallowing impairment specific to FRDA, and to investigate the relationship between dysphagia and disease severity, progression, and genetic make-up. This study is critical in advancing the understanding of FRDA and will elucidate future therapeutic practices to improve the quality and extend the lives of individuals living with FRDA.

In the subsequent chapters, normal and abnormal swallowing will be described followed by a comprehensive analysis of dysphagia assessment and treatment specific to neurodegenerative disease.

Chapter 2 Swallowing and dysphagia

2.1 Introduction

A clear understanding of normal swallowing physiology is necessary to recognise abnormalities in the swallowing process. This chapter describes the phases of normal adult swallowing with reference to swallowing-related anatomy, followed by an appraisal of neurogenic dysphagia (swallowing impairment). Dysphagia in the hereditary ataxia syndromes (including FRDA) is broadly covered and limited empirical data regarding treatment is emphasised as a major clinical issue. This chapter highlights the value of research on dysphagia in individuals with FRDA.

2.2 Normal adult swallowing

Swallowing is the process of passing a substance from the mouth to the stomach to fulfil two vital biological functions: delivering nutrition and hydration, and airway protection (Matsuo & Palmer, 2008). The process includes pre-oral stimulation from the smell, touch, sight, and anticipation of food and liquid (Leopold & Kagel, 1997).

Swallowing relies on finely balanced interaction of conscious and reflexive motor and sensory events (Ertekin & Aydogdu, 2003). It occurs across three anatomical areas: the oral cavity, and pharynx, and the oesophagus (Matsuo & Palmer, 2008). The oral cavity extends from the lips posteriorly to the faucal arches and contains the tongue, teeth, hard and soft palate, and the cheeks. The pharynx lies behind the oral cavity, extending from the uvula to the level of the hyoid bone, and includes the valleculae (the space which lies behind the tongue base and the pharyngeal surface, bounded by the epiglottis). The oesophagus begins at the level of the cricopharyngeal muscle, which relaxes during swallowing to allow food and fluid to pass to the stomach (Logemann, 1983).

Swallowing is broken into phases depending on the location of the bolus, inclusive of the pre-oral phase (Leopold & Kagel, 1997), the oral phase (oral bolus preparation and propulsion), the pharyngeal phase, and the oesophageal phase (Dodds et al., 1990; Matsuo & Palmer, 2009; Logemann, 2014).

2.2.1 Pre-oral phase of swallowing

The pre-oral (or anticipatory) phase of swallowing occurs prior to food or fluid entering the mouth and considers the interaction of motor, cognitive, psychological, and sensory factors associated with eating and drinking (Leopold & Kagel, 1997). These factors precede and

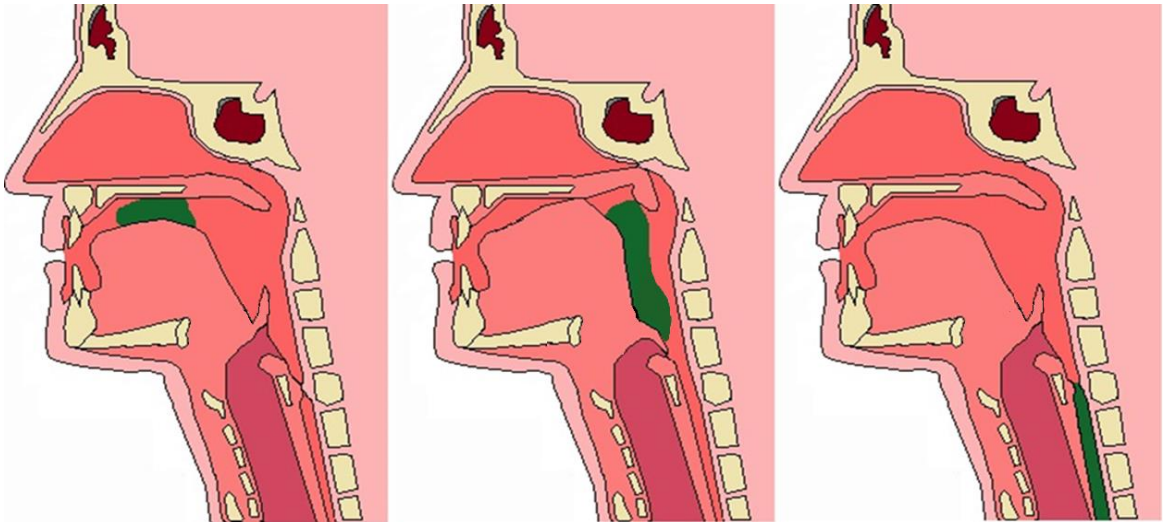
influence the cortically-driven oral phase of swallowing. The key characteristic of the pre-oral phase is sensory acknowledgement that food or drink is present. The sight and smell of food excites salivation which is required later to achieve adequate bolus mastication and preparation (Ekström, Khosravani, Castagnola, & Messana, 2012). Additionally, pre-formed emotional associations with food excite the taste (CN VII, CNX, and CN IX) and olfactory nerves (CN I) (Rolls, 2015). In neurological conditions the pre-oral stage of swallowing may be impaired due to peripheral issues (such as difficulty self-feeding due to upper limb restrictions or positioning), as well as direct degeneration of the central nervous system. Reliance on feeding assistance is a particular consideration and has been identified as a contributing factor of aspiration-related pneumonia (Langmore, Skarupski, Park, & Fries, 2002). Postural difficulties (scoliosis) and associated respiratory compromise may impact on coordination between breathing and swallowing (Holmes, Michael, Thorpe, & Solomonidis, 2003; McFarland, Lund, & Gagner, 1994), further increasing aspiration risk (Martin-Harris, 2006).

2.2.2 Oral phases of swallowing

During the oral phase of swallowing, food or drink is chewed or prepared and transported to the pharynx. The oral phase of swallowing encompasses two stages; preparation and transport (Hiiemae & Palmer, 1999). The oral preparatory stage refers to the process of preparing a bolus to be swallowed and is heavily influenced by pre-oral phase variables including environmental factors, hunger, motivation, taste, and consciousness (Ertekin & Aydogdu, 2003). The motor aspects of the oral preparatory phase are under complete conscious control (Ertekin & Aydogdu, 2003; Watanabe, Abe, Ishikawa, Yamada, & Yamane, 2004). The oral structures coordinate and work together to modify the size and consistency of the bolus appropriately so it can be safely swallowed through the pharynx and oesophagus (Logemann, 2014). Bolus containment within the oral cavity during mastication is achieved by the muscles of the lips (orbicularis oris) and cheeks (buccinators) (facial nerve; CN VII), jaw (trigeminal nerve; CN V, hypoglossal nerve; CN XII) (Hamdy et al., 1997) and the intrinsic tongue musculature (CN XII) (Logemann, 2014). During bolus preparation, mechanoreceptors, chemoreceptors, and thermoreceptors in the mouth and tongue converge in the medulla (the solitary tract and nucleus tractus solitarius, NTS) initiating a motor response specific to the bolus being prepared for swallowing (Ertekin & Aydogdu, 2003; Jean, 2001). The NTS also receives input from the descending cortical pathways (Ertekin & Aydogdu, 2003). When a bolus is ready to be swallowed, it is transported by the tongue

Figure 2-1 - The swallowing process

a) *b)* *c)*



a) The oral phase - transfer of the bolus by the tongue posteriorly towards the pharynx.
b) The pharyngeal phase – demonstrating tongue-to-palate contact driving the bolus posteriorly, velopharyngeal approximation to seal entry into the nasopharynx, epiglottic deflection and opening of the upper oesophageal sphincter
c) The oesophageal phase – the bolus is cleared from the pharynx with no residual matter and passes through the upper oesophageal sphincter. The epiglottis and soft palate are returned to original position.

which moves in a wave like motion, squeezing the bolus against the palate posteriorly towards the pharynx (CN XII) (Logemann, 2014).

The transition between the oral phase and pharyngeal phases of the swallow varies depending on the size and consistency of the bolus. A liquid bolus is held in the oral cavity by sealing off the posterior oral cavity via tongue-to-palate contact (controlled by the contraction of the bilateral palatoglossal muscles, innervated by the glossopharyngeal nerve CN IX) preventing premature entry into the pharynx (Matsuo & Palmer, 2009). However, with solid foods there is usually a gradual accumulation of prepared and masticated food on the posterior surface of the tongue (Ertekin & Aydogdu, 2003) and transfer of the bolus through the fauces and into the pharynx (including to the level of the valleculae) for several seconds before the pharyngeal phase of the swallow is initiated. During this time food often remains in the oral cavity while the subject continues to masticate (Ertekin & Aydogdu, 2003). Thus, the

initiation of the swallow in regards to location of the bolus can vary depending on the substance being swallowed.

2.2.3 Pharyngeal phase of swallowing

The pharyngeal phase of swallowing is largely involuntary (Ertekin & Aydogdu, 2003; Lang, 2009) and refers to events that occur as the bolus moves through the pharynx towards the oesophagus (Lang, 2009). Several processes occur sequentially to prevent entry of material into the nasal cavity and to ensure airway protection during the pharyngeal phase of swallowing (controlled by pattern-generating circuitry of the brain stem). Velopharyngeal closure is achieved by elevation of the soft palate (CN IX and X) which seals the nasopharynx, while the tongue pushes the bolus posteriorly (CN XII), pre-empting contraction of the pharyngeal constrictors (CN X) which directs material towards the pharynx (Ertekin & Aydogdu, 2003). The level of pharyngeal contraction is dependent on the driving force of the tongue (Kahrilas, Logemann, Lin, & Ergun, 1992). Once the bolus has been shifted posteriorly, there is contact between the base of tongue and the soft palate which seals entry into the oropharynx. Laryngeal elevation (CN V, VII, and XII) (achieved via suspension of the suprahyoid muscles) occurs early in the pharyngeal phase of swallowing and facilitates closure of the laryngeal vestibule and repositions the larynx under the base of the tongue (Logemann, 1990). Glottic seal is achieved by closure of the true, false, and aryepiglottic folds, causing a period of apnoea during the swallow (Belafsky & Lintzenich, 2013; Ekberg, 2012; Groher & Crary, 2009). Sensory information from the pharynx (carried by CN V, IX, and X) modulates the level of pharyngeal constriction and determines if extra swallows are required to clear residue. Transient relaxation and opening of the upper oesophageal sphincter is required to allow the bolus to exit the pharynx and is facilitated by contraction of the suprahyoid muscles (laryngeal elevation) (Duranceau, Lafontaine, Taillefer, & Jamieson, 1987).

2.2.4 Oesophageal phase of swallowing

The upper oesophageal sphincter is innervated by the vagus nerve (CN X) (through the pharyngeal, superior laryngeal and recurrent laryngeal nerve branches) (Staller & Kuo, 2013). The period of relaxation of the upper oesophageal sphincter is reported to last between 0.32 to 0.50 seconds (Shaker, 1988). Once the bolus has passed through the upper oesophageal sphincter it moves through the oesophagus towards the stomach via involuntary sequential contractions, known as peristalsis (Paterson & Diamant, 2013). The oesophagus is primarily

innervated by vagal efferent projections from the nucleus ambiguous (NA). Impairment of oesophageal motility can lead to redirection of food or fluids back up towards the pharynx and aspiration into the airway (Logemann, 1998).

2.3 Anatomy of swallowing

2.3.1 Tongue

The tongue has intrinsic and extrinsic muscular components. Four paired muscles originate and insert within the tongue (including the superior longitudinal muscles, the inferior longitudinal muscle, the vertical muscle, and the transverse muscle) and act to control the shape, contour, and action of the tongue to perform oral tasks (Fregosi & Fuller, 1997; Fregosi & Ludlow, 2014; Logemann, 2014). The extrinsic muscles (the genioglossus, hyoglossus, styloglossus, and palatoglossus) make up the majority of the tongue's muscle mass and act to move the tongue within and outside the oral cavity (Logemann, 2014). Extrinsic musculature anchors the tongue to the mandible, hyoid, and cranial base. The genioglossus, the largest tongue muscle, is fan-shaped and widens as it extends the tongue length (Fregosi & Ludlow, 2014). The hypoglossus extends from the body of the greater cornu of the hyoid bone and extends superiorly to the lateral portions of the tongue. The upward and backward movement of the tongue that is necessary for oral bolus propulsion and initiation of the pharyngeal phase of swallowing is achieved via the styloglossus muscle, which extends from the stylohyoid processes of the skull base to the lateral part of the tongue and then to the tongue tip (Matsuo & Palmer, 2008). The styloglossus is innervated by CN XI and CNXII, which also innervate the palatoglossus to raise the back of the tongue whilst lowering the sides of the soft palate (Sawczuk & Mosier, 2001).

During mastication and bolus preparation there is coordination between the tongue, palate, jaw, and lips which allows the tongue to move cyclically to mix food with saliva and contain oral material within the mouth (Logemann, 2014). When the jaw opens, there is lingual movement forward and downward, reaching the most anterior position during mid-to-late jaw opening. This process prevents biting of the tongue during bolus preparation (Matsuo & Palmer, 2008). For both liquids and solids, the tongue acts as a pressure generator to propel material into the pharynx and then the oesophagus where gravity alone is inadequate (Hind, Nicosia, Gangnon, & Robbins, 2005).

The tongue also contains sensory receptors which modulate the swallowing process (Youmans & Stierwalt, 2006). During the oral preparatory and oral propulsion phase, the

tongue provides information regarding the position, volume and viscosity of the bolus, as well as taste information to the medulla (Logemann, 2014; Youmans & Stierwalt, 2006). This information acts to regulate the amount of the bolus to be swallowed and the amount that will remain in the oral cavity (usually pocketed in the buccal cavities) for a second swallow. To retrieve the bolus, the central part of the tongue depresses along the midline as the volume of liquid or food enlarges. This sensory information is fed back to the brainstem and is crucial in the programing the timing of the pharyngeal swallow. The larger the bolus, the sooner the pharyngeal swallow is triggered and the later the tongue base will become activated (Logemann, 2014).

2.3.2 Masticatory muscles

The muscles responsible for mastication are innervated by the mandibular branch of CN V, and include the masseter, temporalis, and medial and lateral pterygoid muscles, which attach to the temporal bone at the temporomandibular joint (Ferrario & Sforza, 1996; Lund, 1991; Pedersen, Bardow, Jensen, & Nauntofte, 2002). The masseter acts to close the jaw as the temporalis muscle moves the jaw upward, forward, and backward. The bilateral medial pterygoid muscles act to elevate the mandible while shifting the jaw to the opposite side unilaterally. The lateral pterygoid muscles move the jaw to the contralateral side unilaterally by pulling downward or forward. The pterygoid muscles work together to allow a grinding action during mastication (Groher & Crary, 2009; Thexton, 1992). CN VII innervates the buccinator muscles compress the lips and flatten the cheeks when food is moved around the oral cavity during the oral preparatory phase. The fibres of the buccinator muscles blend with the orbicularis oris, a complex of muscles that encircle the mouth, allowing for lip seal to be maintained during the swallow (Groher & Crary, 2009).

2.3.3 Soft palate

The soft palate is aponeurotic in structure which allows palatal elevation as the tongue pushes against it during bolus propulsion, drawing the velum superiorly and posteriorly against the nasopharyngeal musculature. This action restricts food and fluid entering the nasal cavity during the swallow (Matsuo, Metani, Mays, & Palmer, 2010; Olthoff, Zhang, Schweizer, & Frahm, 2014). The soft palate acts as an insertion point for the levator veli palantini, which extends from the inferior and lateral surface of the temporal bone close to the foramen of the internal carotid artery, as well as from the inferior surface of the tubal cartilage (auditory canal). From this point, the levator veli palantini extends inferiorly, medially, and anteriorly

to insert into the midpoint of the aponeurosis of the soft palate. The arch of the soft palate is shaped by the palatopharyngeal muscle, which extends from the inferior body of the tubal cartilage, pterygoid processes, and aponeurosis of the soft palate. The palatopharyngeal muscle then extends further inferiorly and posteriorly and forms part of the posterior wall of the pharynx (Groher & Crary, 2009).

2.3.4 Pharynx

The pharynx lies beyond the oral cavity and is formed by 26 pairs of striated muscles innervated by six cranial and four cervical nerves. The pharyngeal musculature is anchored by the hyoid which acts as a fulcrum to provide movement of the posterior tongue, pharynx, and larynx (Groher & Crary, 2009). The nasopharynx, the upper part of the pharynx positioned behind the nose, is sealed during the pharyngeal swallow to stop food or fluid entering the nasal cavity. This seal is formed between the soft palate and the posterior wall of the pharynx (Belafsky & Lintzenich, 2013). This process is regulated by a collection of muscles in the nasopharynx which adjust the position of the muscular palate with respect to the position of the food bolus in the mouth (Campos et al., 2012; Groher & Crary, 2009). These muscles include the palatoglossal and levator veli palantini muscle (innervated by the pharyngeal plexus [CNs IX, X] and accessory nerve [CN XI]), which elevate the palate; the tensor veli palatini (innervated by the mandibular branch of the trigeminal nerve) which tenses the palate and dilates the orifice of the eustachian tube; the palatopharyngeal muscle (innervated by the pharyngeal plexus and spinal accessory nerve) which acts to depress the soft palate and constrict the pharynx; and the muscularis uvula (innervated by the spinal accessory nerve), which acts to shorten the soft palate (Groher & Crary, 2009; D. L. Jones, 2012; Okuhara & Iseki, 2012).

2.3.5 Extrinsic musculature

Hyoid elevation, pharyngeal shortening, and oesophageal opening occur due to the action of the suprahyoid muscles; the digastric, stylohyoid, geniohyoid, and the mylohyoid (Groher & Crary, 2009; Shaw & Martino, 2013). The geniohyoid (innervated by CN XII) draws the hyoid bone upward and forward during the pharyngeal swallow and depresses the jaw. The mylohyoid (CN V) elevates the hyoid bone and the tongue, also depressing the jaw. The anterior belly of the digastric muscle (innervated by the CN V mandibular branch). The posterior portion of the digastric muscle (CN VII) elevates and retracts the hyoid in conjunction with the stylohyoid (CN VII) (Burdett & Mitchell, 2011; Groher & Crary, 2009).

The external muscular pharynx (CN X and XI) consists of the superior, middle, and inferior constrictor muscles. Together these muscles move the bolus toward the oesophagus. This movement is assisted by a pressure system, largely initiated by coordinated interaction of other pharyngeal musculature. These muscles include those which constitute the internal longitudinal layer of the pharynx; the palatopharyngeus, stylopharyngeus, and salpingopharyngeus muscles (Burdett & Mitchell, 2011). The stylopharyngeus muscle (CN IX) elevates the pharynx and the larynx, while the salpingopharyngeus (CN XI) draws the lateral walls of the pharynx upwards (Groher & Crary, 2009).

The oesophageal phase of the swallow is initiated by the relaxation of the cricopharyngeal muscle, a sphincter-like structure that lies at the opening of the oesophagus (Groher & Crary, 2009; Lin et al., 2014). The presence of the bolus above the level of the cricopharyngeal muscle indicates the beginning of the oesophageal phase of the swallow. Innervated by the pharyngeal branches of CN X, the cricopharyngeal muscle relaxes during passage of the bolus from the pharynx into the oesophagus (Groher & Crary, 2009).

2.3.6 Larynx

The larynx marks the opening of the airway. Six cartilages support the larynx, three of which are paired, including the thyroid cartilage, cricoid cartilage (which lines the interior wall of the larynx), and the epiglottis. The unpaired cartilages of the larynx include the arytenoid cartilages (which influence tension of the vocal folds), corniculate cartilages (located at the apex of each arytenoid cartilage), and the cuneiform cartilages (located anterior to the corniculate cartilages). The muscles of the larynx are categorised into intrinsic and extrinsic musculature. The intrinsic muscles of the larynx include the cricothyroid muscles (which manipulate the shape of the vocal folds; external branch of CN X), the posterior cricoarytenoid muscles (which abduct the arytenoid cartilages, achieving vocal fold closure; recurrent laryngeal branch of CN X), lateral cricoarytenoid muscles (recurrent laryngeal branch of CN X) and transverse arytenoid muscles (which adduct the arytenoids; recurrent laryngeal branch of CN X) (Chandra, 2014), the oblique arytenoid muscles (which narrow the laryngeal inlet; recurrent laryngeal branch of CN X), and the thyroarytenoid muscles (which narrow the laryngeal inlet and shorten the vocal folds; recurrent laryngeal branch of CN X) (Groher & Crary, 2009; Jotz et al., 2014). The extrinsic muscles work to depress or elevate the larynx and include the sternothryroid, omohyoid and sternohyoid muscles (all innervated via the ansa cervicalis of the cervical plexus), and the inferior constrictor muscles (pharyngeal plexus; CN X). Muscles that elevate the larynx include the digastric (anterior

belly innervated by mandibular division of CN V via the mylohyoid nerve; posterior belly innervated by CN VII), stylohyoid (CN VII), mylohyoid (mylohyoid nerve, CN V), geniohyoid (CN XII), hyoglossus (CN XII), and the genioglossus (CN XII) (Groher & Crary, 2009; Sasaki, Young, Matsuzaki, & Paskhover, 2014).

Several mechanisms work together to achieve closure of the laryngeal vestibule (Hiss, Strauss, Treole, Stuart, & Boutilier, 2003; Logemann et al., 1992). Epiglottic deflection is achieved by elevation of the hyoid bone (engaging the stylohyoid, digastric, mylohyoid, and geniohyoid muscles) and approximation between the thyroid cartilage and the hyoid bone (by approximation of the thyrohyoid muscle) (Broussard & Altschuler, 2000; Wadie, Adam, & Sasaki, 2013). The epiglottis tilts during laryngeal elevation on the anchorage formed by the pharyngoepiglottic fold. As well, the pharyngeal musculature contraction is thought to contribute to epiglottic tilting (Broussard & Altschuler, 2000).

2.3.7 Saliva

Saliva contains amylase and lipase which are enzymes that assist in the chemical degradation of food (Miller, 2013). Saliva production is under efferent and afferent control, with the salivary systems consisting of numerous glands and secretory rhythms (Ekström et al., 2012; Miller, 2013). It is thought that swallowed saliva from the oral cavity protects the oesophageal wall from being damaged by regurgitated gastric acid (Shafik, El-Sabai, Shafik, & Mostafa, 2005). The salivary glands play a role in body protection against microbes by excreting lysozymes, which kill microbes along with hydrochloric acid secreted by the epithelial cells of the stomach (Miller, 2013).

2.4 Neural control of swallowing

Each phase of swallowing has a different pattern of neurological control. The whole swallow is initiated volitionally via the cerebral cortex and modulated by central and peripheral nervous systems (Mistry & Hamdy, 2008). The reflexive component of the swallow (initiated as the bolus passes to the pharynx) is subconsciously controlled by paired swallowing centres in the medulla (connected to the cortex via descending tracts; the corticobulbar tract) which contains the basic motor plan for swallowing (Mistry & Hamdy, 2008). Emerging evidence also implicates the primary sensorimotor areas during reflexive swallowing (Hamdy, Rothwell, Aziz, & Thompson, 2000).

2.4.1 Cortex

The swallowing cortex is represented bilaterally but asymmetrically (Hamdy, 2006) with each individual having a dominant swallowing hemisphere (Barritt & Smithard, 2009) independent of handedness (Hamdy et al., 1998). Teismann, Dziewas, Steinstraeter, and Pantev (2009) reported a time-dependent shift of neural activation from left to right sensorimotor cortex during deglutition with left hemispheric dominance in the early stage of volitional swallowing and right hemispheric dominance as the swallow proceeds.

Pre-oral and oral phases of swallowing

The action of swallowing follows a conscious decision to accept food or drink. Swallowing initiation is cortically driven, as evidenced by bilateral activation of the caudolateral sensorimotor cortex (Hamdy et al., 1999). Using fMRI Abe and colleagues (2003) reported activation in the cingulate cortex just prior (one to 1.5 seconds) to volitional and is thought to represent initiation and cognitive processing of the swallowing process. Furthermore, additional activation have been noted in the bilateral anterior cingulate gyrus and supplementary motor areas (Abe et al., 2003). The pre-swallowing phase is also associated with activity in the insula and inferior frontal gyrus which continues through the oral phase of swallowing (Dziewas et al., 2003). The primary sensory cortices along with the primary motor cortices appear to have a role in planning and processing the volitional swallow as these activations to not appear during reflexive swallowing (Hamdy, 2006).

During bolus preparation, sensory afferent information is passed from the sensory receptors of the tongue and periodontal area which regulates bolus consistency and bolus propulsive forces to the pharynx (Steele & Miller, 2010). Further sensory information is received from olfaction and gustation of the bolus (Babaei et al., 2010). This sensory input is reported to stimulate activity in the insula, amygdala and orbitofrontal cortex (Leopold & Daniels, 2010). The cortical areas implicated during mastication and driving tongue include the lateral precentral cortex, fronto-operculum, and anterior cingulate cortex (Ertekin & Aydogdu, 2003; Martin et al., 2004). Excitation of the orofacial sensorimotor cortex, pre motor cortex, and posterior and pre-frontal cortical regions has been observed on fMRI for the course of bolus preparation (Steele & Miller, 2010).

Pharyngeal phase of swallowing

Activation of the primary motor cortex has been recorded during the pharyngeal phase of the swallow (investigated using magnetoencephalography; MEG) (Furlong et al., 2004) however

the amount of excitation is task dependent (Doeltgen, Ridding, Dalrymple-Alford, & Huckabee, 2011). Doeltgen and colleagues (2011) measured surface EMG responses of the submental musculature during various swallowing tasks and conditions in response to TMS over the motor cortex in 35 healthy subjects. In that study, motor evoked potentials were more frequently elicited during volitional submental contraction (recorded in 22/35 participants, 62.9%) compared to volitional swallowing (16/22, 45.7%) or triggering a reflexive swallow (7/19, 36.8%). These results indicate that the primary motor cortex assists in controlling and modulating the swallowing process (Doeltgen et al., 2011).

While grossly reflexive, the pharyngeal phase of swallowing regulated by pharyngeal sensory information (Mistry & Hamdy, 2008; Teismann, Steinsträter, et al., 2009). Teismann and colleagues (2009) reported reduced activation in the primary and sensory cortices (as seen on MEG) following application of topical anaesthesia to oropharyngeal structures, with the resulting impaired cortical activity manifesting in reduced speed of swallowing.

2.4.2 Brainstem

The brainstem contains the central pattern-generating circuitry required for the pharyngeal phase of the swallow (Lang, 2009). The neurons involved in swallowing arise from nuclei in the upper medullary and pontine areas of the brainstem (the nucleus tractus solitarius [NTS] and the NA) (Broussard & Altschuler, 2000) and are bilaterally distributed within the reticular formation (Jean, 2001). The NTS receives afferent signals from the oropharynx and larynx and contains the primary sensory nuclei for CN VII, IX and X (Neuhuber & Bieger, 2013). The NTS also receives secondary sensory input via the trigeminal sensory nuclei, located in the pons. The NA contains the primary motor nuclei for CN IX, X and XI, and connects to the NTS via CN V, VII, and XII. The primary sensory nuclei for the superior laryngeal nerve of CN X is located in the NTS and is also connected directly to the NA, which forms the neural pathway responsible for the reflexive cough mechanism (Bieger & Neuhuber, 2006; Neuhuber & Bieger, 2013; Polverino et al., 2012).

2.4.5 Cerebellum

The exact role of the cerebellum in swallowing remains unclear (Rangarathnam, Kamarunas, & McCullough, 2014), however Positron Emission Tomography (PET) and fMRI studies reveal bilateral activation in the cerebellum during swallowing (Suzuki et al., 2003; Zald & Pardo, 1999). Suzuki and colleagues (2003) reported bilateral activation of the cerebellum during saliva swallows on fMRI, with predominant activation in the posterior region of the

left cerebellar hemisphere. Similar findings were revealed by Harris and colleagues (2005) who also observed activation in the left cerebellar hemisphere during volitional swallowing using positron emission tomography (PET). Zald and Pardo (1999) used PET in normal swallowers and observed activation in the Crus Ia/VI region of the left cerebellum. Malandraki and colleagues (2009) provide evidence that the cerebellum may play a role in specific tasks within swallowing. Cerebellar activation was evaluated using fMRI across a series of tasks, including oral controls tasks (tongue tapping and throat clearing), and swallowing water. When compared to the oral control tasks, swallowing water induced activation of the cerebellum, as well as the in thalamus, cingulate gyrus, and the bilateral sensorimotor cortex (Malandraki, Sutton, Perlman, Karampinos, & Conway, 2009).

Animal studies further implicate the cerebellum during swallowing. Zhu, Li, Ding, and Wang (2006) demonstrated altered feeding patterns in rats following cerebellar stimulation, while Satoh, Tsuji, Tsujimura, Ishizuka, and Inoue (2015) found repetitive stimulation of the red nucleus reduced swallow frequency (also in rats). A recent study on humans by Jayasekeran, Rothwell, and Hamdy (2011) demonstrated that distinct motor responses can be induced in the pharyngeal musculature via TMS. The study involved stimulation of the cerebellar hemispheres along with the midline vermis in 16 healthy individuals. The motor evoked potentials measured were significant in the pharynx following cerebellar stimulation, although to a lesser degree following cortical stimulation. Furthermore, when cerebellar stimulation was initiated prior to cortical stimulation, significant facilitation of the motor responses for cortical stimulation was recorded. These results implicate the cerebellum in modulating and intensifying cortical firing for swallowing (Jayasekeran et al., 2011).

2.5 Dysphagia

Dysphagia refers to any abnormality in the transfer of a bolus from the mouth to the stomach and is described by its clinical signs, which may include odynophagia (pain when swallowing), difficulty chewing some or all textures, silent aspiration, and coughing or chocking during and after meals (Ekberg, Hamdy, Woisard, Wuttge-Hannig, & Ortega, 2002). Dysphagia can result from disruption, spasticity, or weakness of the swallowing muscles or from abnormalities of the central and/or peripheral nervous system areas related to swallowing. To assist the diagnostic process, dysphagia is often defined by the anatomical region in which it occurs: oropharyngeal or oesophageal dysphagia (Campisi et al., 2009).

2.5.1 Oropharyngeal dysphagia

Oropharyngeal dysphagia refers to any disruption of passing solids or liquids from the oropharynx to the upper oesophagus (Hurwitz, Nelson, & Haddad, 1975). Symptoms of oral phase dysphagia include leaking of material anteriorly from the lips, laterally into the buccal pouches, or posteriorly into the pharynx (where it may potentially reach the airway if the laryngeal vestibule is not closed). Lingual dysfunction underlies many of the clinical manifestations seen in dysfunction of the oral phase of swallowing, and can delay oral transit of the bolus and impair clearance of the bolus from the oral cavity. Poor lingual control of the bolus may lead to premature spillage over the base of the tongue into the pharynx, increasing the risk of material entering into the airway. A timely pharyngeal swallow response is critical for adequate airway protection, with even a slight increase in bolus dwell time in the pharynx increasing the risk of material entering the airway (known as aspiration) (Butler et al., 2011).

2.5.2 Oesophageal dysphagia

Oesophageal dysphagia is defined as any abnormality occurring as the bolus passes from the pharynx to the stomach, through the oesophagus (Lang, 2013). Oesophageal dysphagia many manifest in odynophagia, the sensation of food or drink being stuck below the level of the upper oesophageal sphincter, or regurgitation of a bolus back into the pharynx. Some common causes of oesophageal dysphagia include achalasia, scleroderma, stricture, tumours, trauma, and oesophagitis (Zerbib, 2014).

2.5.3 Implications of dysphagia

2.5.3.1 Physical health

Individuals with dysphagia are at an increased risk of dehydration, malnutrition, reduced pulmonary function due to respiratory infections (known as aspiration-related pneumonia), and premature death (Ekberg et al., 2002; Threats, 2007). Dehydration may cause sputum to thicken, or reduced saliva production, putting the person with dysphagia at increased risk of respiratory issues (Ekberg et al., 2002; Stringer, 1999), and the likelihood of pathological oral bacteria flourishing and spreading to other parts of the body (Threats, 2007). Malnutrition may manifest in lethargy, impacting on a persons' ability to perform personal hygiene and other activities of daily living (Stringer, 1999).

Aspiration, the inhalation of material from the oropharynx into the larynx and lower respiratory tract (Marik, 2001), is a common sequela of dysphagia. Recurrent aspiration encourages bacterial growth and infection in the lungs, known as aspiration-related

pneumonia; the leading cause of death in some neurodegenerative diseases (Walterfang et al., 2012). Aspiration-related pneumonia is reported to account for 42.02% (166/395) (Sørensen & Fenger, 1992) to 55% (124/224) (Heemskerk & Roos, 2011) of individuals with Huntington's disease (HD), and 45% (236/524) of individuals with dementia (Brunnström & Englund, 2009). Aspiration is also considered a prominent mode of infection in nosocomial pneumonia, especially among the elderly (Langmore, 1996).

Aspiration-related pneumonia presents a diagnostic puzzle. Differentiating aspiration pneumonia from other forms of pneumonia is problematic due a lack of sensitive and specific markers (Marik, 2001). Consequentially, deaths may be recorded as being secondary to 'pneumonia', but may have been due to aspiration and aspiration-related pneumonia specifically (Finucane & Bynum, 1996; Heemskerk & Roos, 2011; Marik, 2001). Silent aspiration, where aspiration occurs without obvious bedside signs of swallowing difficulty, such as coughing or short breath, has been described in many conditions and subgroups, including healthy individuals (Ramsey, Smithard, & Kalra, 2005).

2.5.3.2 Quality of life (QOL)

The presence of dysphagia can limit the social opportunities and pleasure associated with mealtimes, and impact negatively on the relationship between a person with dysphagia and their carer (Ekberg et al., 2002; Stringer, 1999). This has been extensively documented in progressive neurological populations. Leow and colleagues (2010) found that individuals with Parkinson disease (PD) experienced a significant reduction in QOL as a consequence of dysphagia compared to healthy controls, with similar results found in a cohort of individuals with amyotrophic lateral sclerosis (Paris et al., 2013). Dysphagia has also been shown to negatively influence the QOL of individuals with FRDA (Vogel et al., 2014). Significant positive correlations have been established between the dysphagia severity and impairment, activity, and participation restrictions and well-being (Vogel et al., 2014).

2.6 Dysphagia in progressive neurological disorders

Dysphagia is a common symptom of neurodegenerative disease (Walterfang et al., 2012). Werneck and colleagues (2007) reported dysphagia in 53.7% (n=88/251) of individuals with amyotrophic lateral sclerosis, whilst a recent systematic review of the literature (inclusive of 15 eligible papers with a total population of 4510) reported a dysphagia prevalence of 36% of individuals with multiple sclerosis (Guan, Wang, Huang, & Meng, 2015). In PD, dysphagia is reported to occur in 35% of affected individuals (determined in a systematic review,

inclusive of 12 studies) (Kalf, De Swart, Bloem, & Munneke, 2012), and 55% (n=94/243) of individuals with Huntington's disease (case report review) (Guo, Zhang, Burgunder, & Shang, 2010). Despite high prevalence, dysphagia is chronically under-reported in neurodegenerative populations (Bayes-Rusinol et al., 2011). Up to 79.45% (n=470) of individuals with PD were unaware of the presence of swallowing impairment (Bayes-Rusinol et al., 2011). Diagnosis of dysphagia in the PD population often coincides with an initial episode of aspiration-related pneumonia, whereas potentially the individual had symptoms of dysphagia before experiencing respiratory compromise (Manor, Giladi, Cohen, Fliss, & Cohen, 2007).

2.6.1 Dysphagia in FRDA

Dysphagia is common in individuals with FRDA (Vogel et al., 2014) but is poorly understood. No longitudinal studies exist documenting the onset, nature, progression or characteristics of the swallowing deficits in this population. An inverse relationship with GAA1 repeat length has been found for onset of dysphagia (Schöls et al., 1997), however the link between dysphagia severity and size of the GAA repeat has not been investigated. Anecdotal reports suggest individuals with FRDA often choke, require modified foods or alternative feeding (such as nasogastric feeding) as the disease progresses, implying a correlation between disease progression and dysphagia severity (Pandolfo, 2009).

Vogel and colleagues (2014) presented the first detailed study of dysphagia in FRDA and reported dysphagia in 35/36 (97.22%) participants on at least one of four non-instrumental measures of swallowing, including a clinical bedside examination (CBE) and oral motor examination, the Royal Brisbane Hospital outcome measure for swallowing (RBHOMS; describes dysphagia severity in terms of function, independence, and safety), and the Australian therapy outcome measure for speech and swallowing (AusTOMS; a scale of impairment, activity, and participation restrictions, as well as well-being). Thirty-three of the 36 participants (91.76%) presented with clinical signs of dysphagia in the CBE. Dysphagia was shown to impose functional limitations and affect overall QOL in individuals with FRDA. A significant positive correlation was found between the severity of impairment, activity, participation and distress/well-being components of the AusTOMS, suggesting a link between swallowing deterioration and reduced QOL. In addition, a significant relationship was reported between activity restriction related to swallowing impairment and disease duration. No significant correlations were found between dysphagia severity and GAA repeat length, age of onset or disease severity (Vogel et al., 2014).

2.6.2 Dysphagia in the hereditary ataxia syndromes

Dysphagia is a known symptom of HASs (Nilsson, Ekberg, Olsson, & Hindfelt, 1996; Vogel et al., 2014; Vogel, Fendel, Brubacher, Chan & Maule, 2015). Nilsson and colleagues (1996) reported individuals with HASs are at an increased risk of aspiration due to a delayed pharyngeal swallow reflex, based on the VFSS results of eight individuals (two with FRDA). Similar results were reported in a more recent study of 23 individuals with degenerative ataxia (including one with FRDA) (Ramio-Torrenta, Gomez, & Genis, 2006), and a study of 30 individuals with spinocerebellar ataxia (SCA) (da Silva Abdulmassih, Ghizoni Teive, & Santos, 2013). Vogel and colleagues (2015a) reported a dysphagia prevalence of 92% (12/13) in the SCA population, based on results of a retrospective chart audit. In ataxia-telangiectasia (AT), up to 27% (n=14/51) of individuals with the disease are reported to present with aspiration on VFSS, and silent aspiration (whereby there is no reflexive airway protective behaviour elicited) in 71% (n=10/14) of those (Lefton-Greif et al., 2000). When correlated with quantifiable clinical parameters, a significant correlation was seen with age, with those who aspirated being significantly older than non-aspirators ($p<0.01$) (Lefton-Greif et al., 2000).

2.7 Treatment for dysphagia in hereditary ataxia syndromes

High quality evidence pertaining to the treatment of dysphagia in FRDA is lacking (Vogel, Keage, Johannsson, & Schalling, 2015). In a recent systematic review, Vogel and colleagues (2015b) reported an absence of randomised controlled trials (RCTs), or quasi-RCTs investigating dysphagia treatment in the HASs. Given the lack of high quality evidence regarding dysphagia treatment in FRDA current best practice is based on literature from other similar, yet different, conditions (Corben et al., 2014). Common dysphagia management practices recommended in FRDA include postural modification (to reduce the impact of scoliosis), compensatory head positions (such as a chin tuck), adaptive feeding equipment (such as controlled flow drinking containers), and dietary modifications (such as softer food options, blended consistencies, or thickened fluids) (Corben et al., 2014).

2.8 Treatment for neurogenic dysphagia

Treatment for neurogenic oropharyngeal dysphagia may involve compensatory strategies, indirect therapy, or direct therapy (Logemann, 1991). Various dysphagia treatment techniques have been reported in progressive neurological disorders, however the evidence

base remains weak (Ashford et al., 2009; van Hooren, Baijens, Voskuilen, Oosterloo, & Kremer, 2014).

2.8.1 Compensatory swallowing strategies

The aim of compensatory management of dysphagia is to ensure safety of oral intake and provide superficial sensory and kinaesthetic stimulation for swallowing rehabilitation. A secondary aim is to facilitate oral intake in those for whom rehabilitation is ineffective based on aetiology or other pathophysiologic features as is the case with some neurodegenerative groups.

2.8.2 Sensory stimulation

2.8.2.1 Temperature

Thermal stimulation of the oropharyngeal structures has been suggested as a treatment for a delayed pharyngeal swallow (de Lama Lazzara, Lazarus, & Logemann, 1986; Lim, Lee, Lim, & Choi, 2009; Rosenbek, Roecker, Wood, & Robbins, 1996; Teismann, Steinsträter, et al., 2009). Evidence on the efficacy of thermal stimulation in neurogenic dysphagia remains sparse. De Lama Lazzara and colleagues (1986) saw an immediate improvement in swallowing in 23/25 participants (all with neurogenic dysphagia) following cold thermal stimulation, however the long-term effects were unclear. Rosenbek and colleagues (1996) made similar observations in a cohort of 22 patients following stroke, with an immediate improvement seen in the transition swallowing phase following thermal application, however there was insufficient evidence to support or refute the efficacy of cold stimulation as a therapeutic procedure. Regan, Walshe, & Tobin (2010) reported immediate benefits to swallowing function in individuals with PD following application of a Thermo Stim™ device (a long-handled stainless steel tool) which had sat in ice to the anterior faucil arches, when compared to their usual swallowing function. In Regan and colleagues' 2010 study, pharyngeal transit times were reduced in 85% (11/13) of participants on both fluids and paste consistency following tactile-thermal stimulation, and pharyngeal delay times were reduced in 92% (12/13) of participants with fluids and 69% (9/13) of participants on barium paste. Oral transit times were noted to reduce in 92% (9/13) of participants on fluids and in 62% (8/13) of participants on barium paste (Regan, Walshe, & Tobin, 2010). The long-term effects of tactile-thermal stimulation have not been investigated (Regan et al., 2010).

2.8.2.2 Smell, taste, and flavour

The use of smell, taste, and flavour (combination of smell and taste) has shown promising results in the treatment of neurogenic dysphagia. Ebihara and colleagues (2006) reported exposure to black pepper oil for one minute prior to swallowing significantly reduces swallowing latency in 105 individuals with stroke-induced dysphagia. Furthermore, exposure of black pepper oil was shown to increase cerebral blood flow to the insular cortex (Ebihara et al., 2006); a structure implicated in the pre-oral and oral phases of swallowing (Dziewas et al., 2003). Exposure to capsaicinoids has also been shown to benefit clearance of pharyngeal residue and reduce the frequency of laryngeal penetration in a heterogeneous group of individuals with oropharyngeal dysphagia (n=33) (Rofes, Arreola, Martin, & Clavé, 2012). The same group of authors reported positive results using piperine (the alkaloid responsible for black pepper pungency), which was shown to reduce the prevalence of unsafe swallowing and severity of aspiration in 40 heterogeneous dysphagic patients (Rofes, Arreola, Martin, & Clavé, 2014).

Administration of a sour bolus has been shown to improve the oral and pharyngeal latency of the swallow and reduce aspiration in individuals with neurogenic dysphagia (Logemann et al., 1995; Pelletier & Lawless, 2003; Lee et al., 2012). Logemann and colleagues (1995) reported improved timeliness of the pharyngeal swallow following presentation of a sour bolus when compared to a non-sour bolus in individuals post stroke, whist a combination of sour and reduced temperature has been shown to reduce oral and pharyngeal transit times in individuals with stroke-related dysphagia (Cola et al., 2012; Rofes et al., 2014). Furthermore, Pelletier and Lawless (2003) found that citric acid significantly reduced aspiration and penetration compared to water in 11 nursing home residents with neurogenic dysphagia compared to water. Lee and colleagues (2012) found similar results in a cohort of 40 brain injured individuals, where citric acid was shown to significantly lower the incidence and severity of penetration and aspiration.

2.8.2.3 Carbonation

There is limited evidence available to support the use of carbonation in the management of neurogenic dysphagia. Bülow, Olsson, and Ekberg (2003) reported carbonated liquid reduced penetration into the airway when compared to non-carbonated liquid in 40 individuals with dysphagia (36 secondary to neurological impairment) ($p<0.001$). Furthermore, carbonated liquid resulted in significantly reduced pharyngeal transit time ($p<0.001$) and pharyngeal

retention ($p<0.001$). Similar results were reported by Krival (2007), who found individuals following stroke had significantly shorter transition duration and pharyngeal transit time when drinking carbonated liquids compared to drinking thickened fluids (n=14). In contrast, Sdravou, Walshe, and Dagdilelis (2012) reported no significant benefits of carbonated fluids on swallowing (with parameters including oral transit time, pharyngeal transit time, stage transition duration, initiation of the pharyngeal swallow, penetration-aspiration scale, and pharyngeal retention) in a cohort of 17 individuals with neurogenic dysphagia.

2.8.3 Diet Modification

Dietary modification measures, such as altering the consistency and texture of food (pureeing or mashing) and fluid, is a fundamental aspect of dysphagia management (Garcia & Chambers Iv, 2010b; Penman & Thomson, 1998). The extent of diet modification is dependent on the swallowing function of the individual (Garcia & Chambers IV, 2010a). Germain and colleagues (2006) reported a modified diet can assist in maintaining body weight in individuals with dysphagia, although has also been associated with reduced eating desire (Rothenberg et al., 2007). In a cohort of 212 nursing home residents suspected of having dysphagia, Groher and McKaig (1995) reported that altered diets were overprescribed in 92% of those surveyed (31% of the 212 sample). Issues reported in this sample were visually unappealing meals (particularly in the case of pureed foods), lack of taste, and an unpleasant feeling in the mouth (Groher & McKaig, 1995). Enhancing the appearance of modified food (for example, moulding pureed foods into shapes resembling common food items) has been shown to increase oral intake and thus nutritional gain and improve QOL in nursing home residents with dysphagia (Cassens, Johnson, & Keelan, 1996; Germain et al., 2006). Whilst there are benefits to diet modification, Ullrich and Crichton (2015) reported the implementation of diet modification can cause distress for the individual with dysphagia (determined in a cohort of 28 residents, family members, staff and speech pathologists in an aged care setting) and emphasised the importance of managing dysphagia within a client-centred model (de Luis, Aller, & Izaola, 2014).

Fluid viscosity may be modified to manage dysphagia, with the rationale being to reduce the risk of airway entry (Garcia & Chambers Iv, 2010b). However, there have been concerns reported that thickening fluids may result in adverse health outcomes. In a study by Robbins and colleagues (2008), 23% (n=119) of the participant group presented with an adverse medical event, including urinary tract infection, dehydration or fever. The combined outcome of these adverse events was more frequent (albeit that the difference was not statistically

significant) in the group receiving thickened fluids (23 patients versus 12 patients, or 9% compared to 5%) than a participant group receiving unmodified fluids with a chin down posture (p=0.06). A critical review of the stroke literature supported the statement that dysphagic patients on modified fluids are more likely to have poor oral intake and are at an increased risk of dehydration (Affoo & Student, 2008). The decision to recommend thickened fluids for patients with dysphagia should be made on the understanding that patients may experience adverse events.

2.8.4 Postural modification

Postural modifications during swallowing aim to direct the bolus towards the oesophagus in a more efficient manner (Huckabee & Hughes, 2013). Many postural modification strategies have been reported in the literature, including a 'chin tuck' and a 'head turn' whilst swallowing. The 'chin tuck' involves lowering the head to tuck the chin into the chest for each swallow (Ra, Hyun, Ko, & Lee, 2014). The rationale for adopting this position is that it widens the valleculae (Logemann, 1983) and positions the epiglottis in a more posterior position thus narrowing the entry to the larynx (Bülow & Martin-Harris, 2012; Leigh et al., 2014). In a study of 16 healthy participants, adopting a chin tuck was shown to increase the duration of laryngeal vestibule closure when compared to a natural posture (p=0.018). The 'chin down' technique is suitable for individuals with reduced base of tongue function, unilateral laryngeal dysfunction, or delayed pharyngeal swallow initiation (Bülow & Martin-Harris, 2012), but is contraindicated in individuals with weakness of the pharyngeal constrictor muscles as it can increase pharyngeal retention of the bolus, and lead to post-swallow aspiration (Baylow, Goldfarb, Taveira, & Steinberg, 2009; Bülow, Olsson, & Eckberg; Welch, Logemann, Rademaker, & Kahrilas, 1993).

The use of a 'chin tuck' has been shown to eliminate aspiration in 50% of a mixed sample of participants with neurological impairment (Shanahan, Logemann, Rademaker, & Roa Pauloski, 1993). Nagaya and colleagues (2004) reported adopting a 'chin tuck' posture and using supraglottic swallow techniques eliminated aspiration in four of seven participants with cerebellar ataxia, and in one in 13 of individuals with PD. Difficulties arose in individuals with these conditions in achieving the correct posture (Nagaya, Kachi, Yamada, & Sumi, 2004). Logemann and colleagues (2008) investigated and compared the efficacy of the 'chin tuck', unmodified and thickened fluids (both with no 'chin tuck') in a cohort of 711 participants with PD and dementia. Significantly more participants aspirated while adopting the 'chin tuck' strategy (with unmodified fluids) (486/711) compared to nectar thick fluids

(448/711, p<0.001) and honey thick fluids (375/771, p<0.001), however patient preference was heavily weighted towards adhering to unmodified fluids with a 'chin tuck' (Logemann et al., 2008).

2.8.5 Indirect swallowing strategies

Indirect therapeutic strategies are designed to improve the neuromuscular control necessary for swallowing (Logemann, 1993). Such strategies may involve a range of motion or resistance exercises to strengthen the structures used for swallowing (the tongue, jaw, or laryngeal adductors to improve vocal fold closure). Other exercises may involve the patient chewing and manipulating a non-food bolus (Logemann, 1991). Commonly reported indirect swallowing exercises include the Masako manoeuvre (Fujiu & Logemann, 1996), Shaker exercise (Shaker et al., 2002), and various exercises designed to improve oromotor strength. Each exercise is targeted toward a specific dysphagia symptom.

The Masako Manoeuvre

The Masako manoeuvre was developed to improve incomplete tongue base to posterior pharyngeal wall contact or incomplete epiglottic inversion (Fujiu & Logemann, 1996; Prosiegel, Schelling, & Wagner-Sonntag, 2004). The individual is instructed to hold their tongue between their teeth and maintain while swallowing (Fujiu & Logemann, 1996). No studies exist investigating the efficacy of this technique in neurogenic dysphagia, however it has been shown to be beneficial to individuals with head and neck cancer (Lazarus, Logemann, Song, Rademaker & Kahrilas, 2002).

The Shaker Exercise

The Shaker exercise works on simple isometric and isotonic principals to strengthen the suprahyoid musculature. The individual is instructed to lay flat on their back on the floor or bed and hold their head off the floor or bed looking at the feet for a predetermined amount of time (Shaker et al., 2002). In a study of 27 tube-fed individuals with dysphagia (15 secondary to brainstem or hemispheric stroke), completion of the Shaker exercise three times a day over a period of six weeks resulted in significantly reduced pharyngeal residue and post-deglutitive aspiration. Furthermore, all of the 27 participants were able to discontinue tube feeding and no episodes of aspiration-related pneumonia were recorded in the four to 24 months following treatment (Shaker et al., 2002).

Oromotor exercises

Oromotor strengthening exercises are commonplace in clinical practice, however there is limited evidence to support their use in dysphagia treatment (Hind & Robbins, 2013). Isometric lingual exercises (including exercises using a tongue depressor or compressing an air-filled bulb between the tongue and the hard palate) have been reported to improve tongue strength in healthy adults (n=31) (Lazarus, Logemann, Song, Rademaker & Kahrilas, 2002). Similar results were reported by Robbins and colleagues (2005), who found an exercise regime using the Iowa Oral Performance Instrument (Northwest, 2005) increased lingual pressures during swallowing in 10 healthy older individuals (Robbins et al., 2005). Lingual strengthening has been shown to reduce aspiration severity in individuals with post-stroke dysphagia (Robbins et al., 2007). Robbins and colleagues (2007) reported a reduction in the frequency of aspiration following an eight week treatment program of lingual strengthening in 10 individuals post stroke. Three of this cohort underwent MRI of the tongue, of which two showed increased lingual volume after treatment. Substantial gains were also reported on a dysphagia-related swallowing quality of life questionnaire following treatment (Robbins et al., 2007).

2.8.6 Direct swallowing strategies

Direct dysphagia therapy strategies are designed to change swallow physiology. Direct therapy techniques include increased oral sensory stimulation and swallow manoeuvres (Logemann 1991).

2.8.6.1 Swallowing manoeuvres

Various exercises are designed for use while consuming liquids or solids. Such exercises include the supraglottic swallow, the super supraglottic swallow, the Mendelsohn manoeuvre, and the effortful swallow. Use of such strategies in movement disorders is problematic due to difficulty with execution (Nagaya et al., 2004).

Supraglottic swallow

The supraglottic swallow is designed to close the airway at the level of the vocal folds before or during the swallow. To achieve a supraglottic swallow, the individual is instructed to take a breath and hold, then swallow. The individual is then instructed to cough to clear the throat without inhaling, and dry swallow. The supraglottic swallow is primarily designed to compensate for delayed vocal fold closure.

Implementing the supraglottic swallow can be problematic for individuals with neurogenic dysphagia. Cognitive impairment (associated with conditions such as PD and HD) may limit

the individual's capacity to execute the steps necessary to complete the manoeuvre. Fatigue, also a common symptom of neurodegenerative disease, may also limit the functional implementation of the supraglottic swallow over a whole meal. In the stroke population, prolonged voluntary glottic closure is reported to increase the incidence of cardiac complications, such as supraventricular tachycardia, premature atrial contractions, and premature ventricular contractions (Chaudhuri et al., 2002).

Super supraglottic swallow

Like the supraglottic swallow, the super supraglottic swallow is designed to close the airway at the level of the vocal folds, with the main difference being the super supraglottic swallow requires greater effort (Martin, Logemann, Shaker, & Dodds, 1993). The individual is instructed to take a breath and hold, then swallow with maximal effort, cough and swallow again. Like the supraglottic swallow, the super supraglottic swallow facilitates swallowing for individuals with delayed vocal fold closure, but has also been shown to increase the duration of base of tongue to posterior pharyngeal wall approximation.

Mendelsohn Manoeuvre

The Mendelsohn manoeuvre was designed to increase laryngeal motion and improve opening of the upper oesophageal sphincter, and is reported to increase the duration of vertical and anterior movement of the hyoid bone (Logemann & Kahrilas, 1990). The individual is instructed to swallow whilst palpating their thyroid with their finger. The individual is then instructed to swallowing again and consciously hold their larynx in an elevated position for a designated amount of time (Kahrilas, Logemann, Krugler, & Flanagan, 1991). Use of the Mendelsohn manoeuvre is reported to improve swallowing function secondary to neurological disease (Bartolome & Neumann, 1993). In a cohort of 28 individuals with neurogenic dysphagia with concomitant cricopharyngeal dysfunction, 90% made improvements (on objective and subjective measures) following therapy consisting of the Mendelsohn manoeuvre, postural and dietary modification (Bartolome & Neumann, 1993).

Effortful swallow

The effortful swallow involves applying conscious force and squeezing the oral and pharyngeal musculature with greater than normal effort while swallowing. Effortful swallowing has been reported to increase contraction of the submental musculature (Wheeler-Hegland, Rosenbek, & Sapienza, 2008). There is limited evidence supporting the use of an effortful swallow for rehabilitation of neurogenic dysphagia. Park, Kim, Oh, and Lee (2012)

reported a combination of effortful swallow and electrical stimulation treatment increased vertical laryngeal displacement in individuals with post-stroke dysphagia (n=20). Effortful swallow was reported to have little effect on intrabolus pressure and duration in eight dysphagic individuals (including six participants post stroke) (Bülow, Olsson, & Ekberg, 2002).

2.8.7 Surface electrical stimulation

Surface electrical stimulation (SES) to the submental and laryngeal areas has been demonstrated to alter the patterns of swallowing (Ludlow et al., 2007) however the effectiveness of SES as a treatment for dysphagia remains unclear. Baijens and colleagues (2013) investigated the efficacy of SES in 90 individuals with PD quasi-randomly assigned into three groups and received 30 minutes of therapy daily over 15 days. All groups received traditional treatment, inclusive of swallowing manoeuvres, postural modifications, and food and fluid modification. Motor level stimulation was applied to group 2, whilst group 3 received sensory level stimulation. Few significant effects were observed in dysphagic PD patients after a single session using different electrode positions. Furthermore, little benefit was noted on QOL measured and VFSS in SES compared to traditional dysphagia treatment (including airway-protecting manoeuvres, postural compensation manoeuvres, bolus modification and oral intake of various foods, swallowing saliva, and oral motor exercises) (Baijens et al., 2013; Heijnen, Speyes, Baijens, & Bogaardt, 2012).

2.9 Summary

Swallowing is a complex, finely balanced action involving careful coordination of several muscles, sensory, and motor systems (Steele & Miller, 2010). Impaired swallowing, or dysphagia, can manifest in detrimental physical and psychosocial health consequences. Dysphagia is an expected complication of various neurodegenerative diseases and can be fatal in these conditions. Anecdotal evidence and emerging empirical evidence suggest a significant prevalence of dysphagia in individuals with FRDA, however detailed studies investigating FRDA-related dysphagia in line with the current clinical standard of swallowing assessment are lacking. Critically, the evidence base of treating and managing FRDA-related dysphagia is weak. The project described in this thesis aims to address this gap in the literature, by providing a clear understanding of the characteristics of swallowing impairment in individuals with FRDA.

Chapter 3 Dysphagia assessment in progressive neurological disorders

3.1 Introduction

Clinical evaluation of swallowing encompasses both bedside (non-instrumental) and instrumental methods. The clinical beside examination (CBE) includes a detailed case history, evaluation of oral motor and sensory function, and trials of food or drink. Instrumental assessment, including videofluoroscopic evaluation (VFSS) and fibreoptic endoscopic evaluation (FEES), provides an objective evaluation of swallowing function. This chapter reviews the CBE and instrumental swallowing assessment techniques appropriate for use in the neurodegenerative population. Subjective swallowing questionnaires are also reviewed to identify which approach is more effective for individuals with progressive neurological disease (Keage, Delatycki, Corben, & Vogel, 2015).

3.2 Patient history

A patient case history provides valuable information on the onset and progression of swallowing difficulties, and the presence of influencing factors (Denk-Linnert, 2012). Details of any previous dysphagia intervention is also collected (McCullough & Martino, 2013). Furthermore, the patient history provides information regarding cognition, motor speech function, language function, or other relevant neurological issues such as dyskinesia or dystonia (Denk-Linnert, 2012; Prosiegel, 2012). Subjective swallowing assessments probe for some of this information and are appropriate for use in progressive neurological populations (Keage et al., 2015).

3.3 Clinical bedside examination of swallowing (CBE)

The CBE is an important first step of swallowing assessment (Jaradeh, 2013; Ramsey, Smithard, & Kalra, 2003; Speyer, 2013; Wiemer, 2015). The CBE allows confirmation of dysphagia (Speyer, 2013; Wiemer, 2015) and informs therapeutic and management strategies (Maccarini et al., 2007; McCullough & Martino, 2013; Speyer, 2013). For individuals presenting with pre-confirmed dysphagia, the CBE functions to monitor swallowing status and modify management accordingly (McCullough & Martino, 2013). A detailed case history is collected in the CBE and should probe for information pertaining to the onset, duration, frequency, and description of dysphagia symptoms (McCullough & Martino, 2013). Motor and sensory function of the swallowing mechanism is also evaluated via a series of directed tasks and while the patient is eating and drinking (Carnaby-Mann & Lenius, 2008; McCullough & Martino, 2013).

3.3.1 Assessment of motor and sensory function

Disrupted motor and sensory function of the swallowing mechanism is an expected sequela of neurodegenerative disease, necessitating the need for comprehensive assessment (Daniels, 2006; González-Fernández, & Daniels, 2008). Upper and lower motor neuron degeneration (particularly of the cranial nerves [CNs] required for swallowing - V, VII, IX, X, and XII) can manifest in impaired motor control of a bolus (Daniels, 2006; Ruoppolo et al., 2013), while disturbed laryngeal sensitivity can stifle the reflexive cough reflex, such is the case in PD (Mu et al., 2013) and Multiple Sclerosis (MS) (Wiesner et al., 2002).

Facial musculature

To assess facial musculature (CN V, VII) the patient is directed to perform a series of tasks, including pursing and retracting the lips or prompting the patient to open and close the jaw against resistance (McCullough & Martino, 2013).

Lingual function

Examination of lingual function (CNXII) includes observation of tongue protrusion, lateralisation, elevation, and tongue pressure against a tongue depressor (Lazarus et al., 2003).

Palatal function

The palate (CN IX/X) is assessed for signs of atrophy. Palatal symmetry is considered during phonation, along with palatal elevation, achieved by directing the patient to produce a prolonged /a/ (“ah”). Palatal function during swallowing (nasopharyngeal approximation) is impossible to assess at the bedside and can only be determined using VFSS (Mann & Hankey, 2001).

Laryngeal function

The presence of dysphonia (a manifestation of laryngeal dysfunction) is significantly related to aspiration in the acute stroke population (Daniels et al., 1998; Horner, Massey, & Brazer, 1990). Voice quality is evaluated by eliciting a prolonged vowel (“ah”) (McCullough & Martino, 2013). The presence, quality (wet or dry) and strength of the volitional cough is also determined (McCullough & Martino, 2013).

3.3.2 Oral trials

The inclusion of food and drink trials is at the discretion of the clinician (Carnaby-Mann & Lenius, 2008). Administration of food or drink (including the type and amount), is also determined by the clinician in lack of a standard protocol (Kertscher, Speyer, Palmieri, & Plant, 2014). Bedside examination of oral intake informs the clinician of the patient's ability to contain food or fluid in the mouth, the ability to manipulate and shift a bolus posteriorly, the presence of hyolaryngeal excursion, and the effectiveness of oral clearance.

3.3.3 Limitations of the CBE

The reported sensitivity and specificity of CBE components for identifying aspiration is varied. Horner and colleagues (1990) reported sensitivity ranging from 67% to 97%, and specificity from 29% to 70% (confirmed on VFSS) for a range of bedside oral motor examinations (including cough quality, dysphonia, and gag reflex) in 70 individuals following stroke. Similar results were reported by Stanners, Chapman, & Bamford (1993), where the same group of examinations yielded sensitivity values ranging from 60% to 70%, and specificity of 45% to 78% (n=50 individuals post stroke). In a study by Leder and colleagues (2013) of 3,919 individuals following stroke, the presence of facial asymmetry was shown to increase aspiration risk by 0.76 (95% CI=0.61-0.95, p=0.017), while the presence of lingual dysfunction increased the odds of aspiration by 2.72 (95% confidence interval =1.96-3.79, p<0.0001). Daniels and colleagues (1998) reported the presence of volitional cough and cough with swallow, in conjunction, predicted aspiration with 78% accuracy in the acute stroke population as determined by Videofluoroscopic Study of Swallowing (VFSS) (calculated via stepwise logistic regression). In a cohort of 60 individuals post thromboembolic stroke, evaluation of volitional cough strength had a sensitivity of 0.700 and specificity of 0.240 (X^2=1.250), while evaluation of cough quality had a sensitivity of 0.545 and specificity of 0.684 (X^2=3.062) in predicting aspiration (McCullough, Wertz, & Rosenbek, 2001). A judgement regarding the presence of aspiration based on oral trials alone is shown to miss up to 40% of individuals who aspirate in the stroke (Lim et al., 2001). In a mixed neurological population (n=93, including 28 post stroke, seven following traumatic brain injury, seven with MS, 27 with PD, 6 with ALS, five with myotonic dystrophy, two with progressive supranuclear palsy, two with olivopontinocerebellar atrophy, and three with FRDA) a 90ml water test was reported to have a limited sensitivity of 52% and specificity of 86% for detecting aspiration (Mari et al., 1997). According to McCullough and colleagues (2001), the presence of a spontaneous cough

during test swallowing (sensitivity 0.682, specificity 0.816, X^2=14.857) and an overall estimate regarding the presence of aspiration based on clinician's judgement (sensitivity 0.773, sensitivity 0.791, X^2= 14.857) are the most reliable components of the CBE in predicting aspiration (based on a review of the components of CBE in 60 individuals following stroke). In the same study, the presence or absence of decreased speech intelligibility, secretion management, and volitional cough correlated with the presence of dysphagia. Voice resonance and the presence or absence of a wet vocal quality also demonstrated strong sensitivity and specificity. With oral trials, the only reliable predictors of dysphagia were the presence of a spontaneous cough during the swallow, and an overall estimate of aspiration (therefore relying on the clinician's clinical judgement) (McCullough et al., 2001).

Other limitations of the CBE arise due to environmental factors. The CBE is performed in a medical setting, with little talking, and the patient is required to eat food that they may not consider appealing. Threats (2007) compares this clinical setting with a more natural and social setting, where there is often talking when eating and drinking and the food available is likely to be more appealing than that offered in the clinical setting. The experience and performance of eating and drinking are markedly different between these two settings (Threats, 2007) limiting the ecological validity of the standard CBE.

The CBE serves an important role in the assessment of dysphagia and should not be discredited (McCullough et al., 2001). The CBE allows for the clinician to make recommendations regarding feeding position, the amount of oral intake appropriate for the individual, eating duration, and necessity for adaptive feeding equipment. Limited sensitivity and specificity means the CBE cannot be reliably used to detect aspiration, necessitating the need for instrumental analysis of swallowing (Ramsey, Smithard, & Karla, 2003) (described further in 3.5 Instrumental analysis of swallowing).

3.4 Instrumental analysis of swallowing

Instrumental analysis (VFSS and FEES) are the current clinical standard of swallowing assessment (Brady & Donzelli, 2013; Rugiu, 2007). Instrumental analysis informs understanding of the physiological and mechanical aspects of swallowing to develop an overall impression of dysphagia severity. Instrumental analysis should always be used in conjunction with the CBE, however due to the difficulty detecting silent aspiration the CBE cannot replace instrumental analysis (Denk-Linnert, 2012).

3.4.1 Fibreoptic Endoscopic Evaluation of Swallowing (FEES)

FEES involves the passing of an endoscope through the nasal cavity, past the velopharyngeal boarder and into the pharynx to obtain a direct view the surface structures of the lower pharynx and laryngeal vestibule (Kidder, Langmore, & Martin, 1994). The endoscope is flexible and can be manoeuvred easily to achieve a better view of the swallowing structures. The endoscope is attached to a camera for real-time viewing and recording for benchmarking and on-going monitoring.

Advantages of FEES

FEES is the preferred method of assessment when direct observation of the pharyngeal and laryngeal vestibule surface anatomy is required. Pharyngolaryngeal pathology, including oedema, erythema, and lesions can be viewed directly. An impression of the patient's ability to self-manage secretions can also be made. FEES allows for direct observation of the passage of the bolus through the hypopharynx and the presence of any post swallow residue. FEES is more accessible than other forms of instrumental swallowing analysis due to the portable nature of the machinery and the flexibility in terms of the patient's positioning. Furthermore, FEES does not require food to be mixed with a contrasting agent (such as barium in the case of VFSS) which is less imposing to the patient (Langmore, 2011).

Limitations of FEES

FEES does not allow for detailed observation of the passage of the bolus from the mouth to the stomach. The oral phase of the swallow is not viewed on FEES and hyoid movement is implied rather than directly observed (which is possible on VFSS). At the height of the swallow, the view of the hypopharynx is lost due a phenomenon known as 'white out', caused by approximation of the tongue and pharynx reflecting the light from the top of the endoscope back up to the camera. This prevents view of the bolus movement at this point and penetration and aspiration cannot be detected, making quantification of airway entry is impossible in FEES assessment. Further, FEES does not allow for a view of the cricopharyngeus and upper oesophageal sphincter (Wiemer, 2014).

3.4.2 Videofluoroscopic Study of Swallowing (VFSS)

The VFSS (also referred to as the Modified Barium Swallow, or MBS) allows for complete and dynamic evaluation of all phases of swallowing as the bolus passes through the oral cavity, pharynx, and past the upper oesophageal sphincter on its way to the stomach (Rugiu, 2007). The VFSS is a radiological investigation using fluoroscopic images that can be viewed

in real-time on a monitor attached to the fluoroscopic machine (Rugiu, 2007). The VFSS allows the clinician to form impressions of the patient's swallowing efficiency and safety, test the efficacy of swallowing compensatory strategies, recommend an appropriate diet, and recommend appropriate rehabilitative techniques. VFSS is the preferred tool to comprehensively assess the oral, pharyngeal, and oesophageal phases of swallowing (Daniels & Huckabee, 2014; Groher & Crary, 2009; Martin-Harris et al., 2008; Martin-Harris & Jones, 2008).

Clinical indications for VFSS include the need for an objective view of swallowing anatomy and physiology, evaluation of the presence and frequency of aspiration and severity of residue, or to define the physiological causes underlying any symptoms suggestive of dysphagia. In addition, VFSS allows the clinician to make a judgement about the safest and most appropriate food and drink consistency for the individual (Crary, 2009; Perlman, Lu, & Jones, 1997; Martin-Harris et al., 2008; Rugiu, 2007). VFSS is not recommended for medically unstable patients who cannot participate in the procedure, or patients unable to be positioned correctly in the fluoroscopy machine (Crary, 2009).

The VFSS is conducted in a specialised fluoroscopy radiology suite, using a fluoroscopic tube. Normally present in the radiology suite is a speech pathologist, radiologist, and radiographer (along with the patient) (Logemann, 1998). The field covered by the VFSS encompasses the oral cavity (including the anterior surface of the lips to make judgement of lip seal adequacy), pharynx, larynx, and the upper oesophagus. VFSS allows for delineation of anatomical structures and possible abnormalities, such as bars, webs, strictures, rings, hypopharyngeal diverticuli, hiatal hernias, oesophageal dysmotility, and reflux. VFSS should be performed with the participant positioned in their most natural position, so to replicate everyday feeding practices. Participants should also be encouraged to self-feed for swallowing function to be most demonstrative of the person's ability. The participant is positioned next to the fluoroscopy tube in the lateral view, allowing for easy identification of anatomical reference points. During VFSS, various quantities and consistencies of barium contrast material are administered to the participant.

Contrasting agents used in the VFSS can alter the nature of the food and fluid being trialled. Adding barium to a liquid can cause the liquid to thicken and change the dynamic properties of the liquid, and mask the properties of faster flowing liquid. In addition, the presence of barium can increase the likelihood of pharyngeal residue being present after the swallow (Hind et al., 2012; Steele, Molfenter, Péladeau-Pigeon, & Stokely, 2013). Fink and Ross

(2009) compared one commercially available liquid barium produced (E-Z-EM's Varibar®) to ultra-thin liquid, and found that 50% of a 40-strong participant group aspirated on the ultra-thin liquid but did not aspirate on the Varibar® liquid. Despite the Varibar® being considered "thin", it was not thin enough to elicit aspiration. Similar results were replicated in studies by Stuart and Motz (2009), Strowd, Kyzima, Pillsbury, Valley, and Rubin (2008), and Costa, Almeida, Sant'Anna, and Pinheiro (2007). This highlights the importance of standardising barium recipes when conducting VFSS to replicate an accurate portrayal of the person's swallow.

Advantages of VFSS

The use of VFSS over, or in conjunction with, other forms of instrumental swallowing assessment is advantageous as it is conducted in real-time, allowing for visualisation of the current movement of the bolus from the lips to the oesophagus (Martin-Harris et al., 2008). VFSS is the only form of instrumental swallowing assessment that allows for observation of the swallowing structures and their function (Crary, 2009), and the amount, severity, and timing of aspiration (Mann & Hankey, 2001). VFSS can be recorded and used to provide education to the patient and their family or carer, the medical team, or to compare swallowing function over time.

Limitations of VFSS

Although the current clinical standard of dysphagia assessment (Evatt et al. 2009), instrumental analysis is a poor measure of overall functional disability. Thus recommendations based on instrumental analysis alone may lead to a management approach with little practicality to the patient (Threats, 2007). VFSS should always be considered a 'snapshot' of swallowing ability, and may not always be reflective of the patient's true performance over an entire meal. Additionally, the VFSS is conducted in a clinical setting which is not representative of the patient's home environment. Threats (2007) highlights the stark differences between this setting and the normal eating environment where there is usually social distraction and none of the stressors that come with being in an unfamiliar laboratory environment. Additionally, the presence of barium can be unpleasant for some patients and lessen the desire for food and drink (Cichero, Jackson, Halley, & Murdoch, 2000). The variability in the reliability, implementation and interpretation also act a significant barrier when implementing VFSS (McCullough et al., 2001; Karnell & Rogus,

2005; Scott, Perry, & Bench, 1998). The use of radiation may also limit the capacity for repeat VFSS procedures.

3.4.2.1 Standardising the VFSS

The VFSS is not standardised in clinical practice (Speyer, 2013) leading to ambiguity of reporting, inaccuracies in assessment and selection management strategies, and inconsistency of service delivery between the treating clinicians (Martin-Harris et al., 2008; Speyer, 2013). Standardisation may take the form of controlling the type and size of the boluses delivered during the VFSS. To completely standardise the procedure would be difficult due to the wide variety of clinical aetiologies that can result in dysphagia.

Establishing consensus in VFSS rating is problematic (Stoeckli, Huisman, Seifert, & Martin–Harris, 2003). Baijens and colleagues (2013) identified 19 papers pertaining to intrarater and interrater reliability for measurements in VFSS. The methodology used during the VFSS procedure varied greatly, and in turn the reliability carried with the method of measurement. Studies differed in terms of the method of bolus delivery (including type and frequency of the boluses), and the level of training of the raters. This review found that intrarater agreement was more reliable than interrater agreement, and methods of measurement using well-defined spatial variables showed better reliability overall (interrater and intrarater). Two studies identified in this paper highlighted the importance of pre-experimental training and consensus scoring for judges improved the reliability of the measurements (Pauloski, Rademaker, Kern, Shaker, & Logemann, 2009; Scott, Perry, & Bench, 1998). Scott, Perry, & Bench (1998) investigated interrater reliability between nine Speech Pathologists with varying levels of experience using a five point scale. The authors reported interrater reliability was lowest when raters worked independently interpreting the scale alone. The highest level of agreement was reached when judges were able to discuss their decisions and form consensus. When judges were instructed to rate the VFSS independently after a group discussion, the level of agreement weakened. Other factors which improve interrater agreement included a clearly stipulated point of assessment (during consecutive swallows, for example), the quality of the image, the capacity for slow reply, and the consistency of the bolus being trialled (thickened fluids which moved slower through the oropharynx were deemed easier to rate). Similar recommendations were made by Pauloski and colleagues (2009), who emphasised the importance of image quality, establishment of rules for measuring, and the opportunity for regular discussions among raters to achieve consensus. The review by Baijens, Barikroo, and Pilz (2013) also highlighted the variability in the scale being used to quantify VFSS. Some

studies used ordinal visuoperceptual variables, such as the Penetration-Aspiration Scale by Rosenbek, Robbins, Roecker, Coyle, and Wood (1996), while other studies used continuous spatial and temporal variables.

3.5 A systematic review of self-reported swallowing assessments in progressive neurological disorders

A Systematic Review of Self-reported Swallowing Assessments in Progressive Neurological Disorders.pdf

Chapter 4 Study 1 - Swallowing-related quality of life in individuals with Friedreich ataxia

4.1 Research questions

Dysphagia is known to present significant challenges for individuals with FRDA, including reduced ability to participate in social gatherings and overall quality of life (QOL) (Vogel et al., 2014). In other neurogenic populations, dysphagia is associated with social withdrawal (Chow et al., 2004; Ekberg et al., 2002), depression (Chow et al., 2004; Farri, Accornero, & Burdese, 2007), and panic and anxiety associated with mealtimes (Ekberg et al., 2002). Currently, there are no studies that describe swallowing-related QOL in individuals with FRDA using a standardised self-directed measure, or compared with a group of healthy age-matched controls. In addition, the relationship between swallowing-related QOL and FRDA disease progression is unknown. These knowledge gaps raise the following questions:

1. What is the impact of dysphagia on the quality of life of individuals with FRDA?
2. How does swallowing-related QOL relate to FRDA disease parameters, including age at symptom onset and assessment, disease duration, *FXN* intron 1 GAA repeat sizes and Friedreich Ataxia Rating Scale (FARS; Subramony et al., 2005) score?

4.2 Aims and hypotheses

Aim 1: To determine the impact of dysphagia on the QOL of individuals with FRDA.

Hypothesis: Individuals with FRDA will record reduced swallowing-related QOL factors when compared with a group of age-matched healthy controls, in line with previous studies in neurodegenerative populations such as Parkinson's Disease (PD) (Leow, Huckabee, Anderson, & Beckert, 2010; Plowman-Prine et al., 2009) and Amyotrophic Lateral Sclerosis (ALS) (da Silva Abdulmassih et al., 2013).

Aim 2: To determine the relationships between swallowing-related QOL and FRDA (including age at symptom onset and assessment, disease duration, FXN intron 1 GAA repeat sizes and Friedreich Ataxia Rating Scale [FARS; Subramony et al., 2005] score).

Hypothesis: Reduced swallowing-related QOL will be experienced more acutely by individuals with more severe disease and in the later stages of disease progression. The presence of FRDA-related dysphagia will correlate with disease parameters in line with previous research (Vogel et al., 2014).

4.3 Rationale

Chronic dysphagia imposes significant psychosocial burden and negatively impacts on QOL (Chow et al., 2004; Ekberg et al., 2002). Dysphagia is prevalent in the FRDA population and is known to impose significant restrictions in terms of social participation (Vogel et al., 2014). In the present study, the psychosocial impact of FRDA-related dysphagia was investigated using a standardised questionnaire, the Swal-QOL (McHorney et al., 2000). Additionally, the relationship between FRDA progression and severity and dysphagia-related QOL was explored to better inform dysphagia management in this population.

4.4 Background

Dysphagia is a chronic condition associated with significant social and psychosocial burden and reduced QOL (Eslick & Talley, 2008; Vesey, 2013). Dysphagia affects eating and drinking and imposes significant health risks including malnutrition, dehydration, and aspiration-related pneumonia (Ekberg et al., 2002). Although the majority of individuals with dysphagia can continue to eat and drink safely facilitated by modified oral intake or implementation of safe swallowing strategies, the fear of eating or the effort involved may reduce the pleasure associated with mealtimes. Individuals with dysphagia may also experience embarrassment associated with the condition and as a result often avoid eating and drinking in the presence of others and avoiding social events (Ekberg et al., 2002; Threats, 2007). In the case of neurodegenerative conditions, difficulty feeding and fatigue may further restrict mealtime participation and reduce satisfaction with eating (McHorney et al., 2000). Dysphagia also imposes significant burden on family and carers of the person affected (Penner, McClement, Lobchuk, & Daeninck, 2012). Dysphagia is reported to impact on the social activities of carers, such as participation in shared meals (Patterson, Rapley, Carding, Wilson, & McColl, 2013).

Considering the impact of dysphagia beyond physical health complications warrants a holistic management approach with collaboration between the patient, Speech Pathologist, and multidisciplinary treating team. The use of a subjective, patient-driven assessment of dysphagia has been advocated for in the existing literature (Belafsky et al., 2008; Keage et al., 2015; McHorney et al., 2000) and provides insight into the patient's perceptions of dysphagia and impact on QOL.

Vogel and colleagues (2014) present the largest study to date investigating FRDA-related dysphagia and QOL. Data on the swallowing function (including diet modification and other

compensatory swallowing strategies) of 36 individuals with FRDA (mean FARS 95.23) were collected via a series of bedside swallowing measures, including a CBE, oromotor examination, the Royal Brisbane Hospital outcome measure for swallowing (RBHOMS), and the Australian Therapy Outcome Measures for Speech and Swallowing (AusTOMS). The RBHOMS describes the presence of swallowing difficulties and changes in swallow function over time, while the AusTOMS is a tool used specifically for assessment of patient outcomes in the context of activity, participation and well-being as outlined in the WHO ICF framework. Dysphagia was recorded on at least one measure in 35/36 (97.22%) of the participants. Thirty-three of 36 (91.66%) participants exhibited clinical signs of dysphagia on CBE, including coughing and choking on fluids (21/36, 58.33%) and dry or crumbly foods (14/36, or 38.89%). Dysphagia strategies were employed by 19/36 (52.78%) of the participants, and included concentrating on components of swallowing such as mastication, respiratory coordination, and tongue movement. Eight of the 33 (24.24%) participants who exhibited dysphagia on CBE modified the texture of their diet. On AusTOMS, 19/36 (80.6%) presented with a degree of function loss secondary to dysphagia, with a significant difference reported between the impairment ratings of the modified and normal diet groups ($p<0.05$). Data from the RBHOMS revealed 30/36 (83.34%) participants received a score indicating the need for supervision with meals, compensatory strategies, or diet modification. On oromotor-examination, voluntary lingual movements (CN XII) were most commonly impaired, with no significant difference observed in CN XII function between participants on a modified diet and those on an unmodified diet. Via spearman rank correlations the authors revealed a significant relationship between the activity rating on the AusTOMS and disease duration ($\rho=-0.28$, $p<0.05$). Further correlations were reported between impairment and other domains assessed on the AusTOMS, with activity limitation ($\rho=0.62$, $p<0.01$), participation restriction ($\rho=0.44$, $p<0.01$), and distress/wellbeing ($\rho=0.50$, $p<0.01$). GAA repeat length, age at disease onset, and disease duration were not shown to relate to the presence of dysphagia (Vogel et al., 2014).

Despite being the largest study of FRDA-related dysphagia, the study by Vogel and colleagues (2014) is limited as it did not compare individuals with FRDA and age-matched healthy controls, and the measures used were clinician driven. The present study adds to the study by Vogel and colleagues (2014) using a comprehensive, standardised questionnaire (the Swal-QOL) to evaluate swallowing-related QOL in FRDA. A recently published review of self-reported swallowing questionnaires (Keage et al., 2015) (included in Chapter 3)

identified the Swal-QOL as the most appropriate for use in the progressive neurological population as it yields a strong combination of reliability (including internal consistency and test–retest reliability), validity, and clinical application (including adherence to the WHO's International Classification of Functioning, Disability and Health (WHO ICF) framework) (Keage et al., 2015).

4.5 Methods

4.5.1 Participants

Sixty individuals with FRDA were recruited from the Friedreich Ataxia Clinic (Monash Health, Melbourne, Australia). Individuals were excluded if they had a history of concurrent unrelated neurological disease, or the presence a speech and/or swallowing disorder prior to the onset of FRDA. All participants were provided with the Swal-QOL questionnaire and 59 were returned (one participant did not return the questionnaire, and therefore their clinical data was not used). All participants were able to read the questionnaire independently. Where upper limb ataxia prevented the participant filling in the questionnaire themselves, a proxy (typically a carer or family member) was appointed. Refer to Table 4.1 for the demographic and clinical characteristics of the FRDA group.

A group of 60 healthy controls (HC) (35 female, 25 male) were recruited for comparative data via advertisement (posters) around The University of Melbourne Parkville campus and by word of mouth. Exclusion criteria covered neurological impairment, pulmonary disease, or history or neck surgery. There were no significant differences between the mean ($\bar{x}$) age between the two groups (FRDA: mean ($\bar{x}$) age 35.49 years, standard deviation (σ) 12.21; HC: $\bar{x}$ age 38.34 years, σ 17.36 years, range 16.14 to 90.63 years; $p>0.05$).

Table 4-1 Demographic and clinical characteristics of the FRDA group

ID	Age at disease onset	Gender	GAA1	GAA2	FARS	Age (years)
FA001	13	Female	706	811	106.5	43.3
FA002	5	Male	1099	1099	N/A	39.6
FA003	24	Male	682	1041	96	45.5
FA004	25	Female	284	984	78	47.9
FA005	14	Male	720	720	66	29.7
FA006	15	Male	720	720	68	29.7
FA007	3	Male	645	771	127.5	38.0
FA008	14	Female	760	1020	117	50.8
FA009	14	Male	471	590	74.5	23.3
FA010	14	Male	552	552	71.5	29.8
FA011	11	Female	444	526	70.5	22.2
FA012	14	Male	650	900	129	44.6
FA013	18	Female	447	967	102	31.4
FA014	18	Male	374	985	66	29.0
FA015	8	Female	642	1132	136	39.3
FA016	28	Male	606	986	102.5	53.9
FA017	20	Female	646	1293	115.7	49.6
FA018	11	Female	659	865	108.5	22.2
FA019	9	Female	694	1000	119	23.6
FA020	23	Male	291	912	37.5	32.1
FA021	7	Male	780	980	138.5	50.7
FA022	34	Male	126	924	71.5	55.5

FA023	10	Male	659	822	109.5	25.8
FA024	12	Male	850	850	N/A	49.3
FA025	13	Female	471	707	130.5	36.8
FA026	32	Male	320	320	70.5	41.1
FA027	26	Male	560	989	N/A	51.0
FA028	19	Male	476	545	76.5	37.4
FA029	14	Female	833	835	95.5	31.7
FA030	6	Male	815	856	N/A	15.5
FA031	12	Female	685	1064	41	18.2
FA032	14	Male	569	884	77	23.6
FA033	30	Male	323	1046	66	49.6
FA034	21	Female	462	462	84.5	38.8
FA035	14	Female	727	727	90.5	33.6
FA036	30	Female	414	590	63.5	34.7
FA037	3	Male	800	800	109.5	21.3
FA038	21	Female	437	611	N/A	23.3
FA039	8	Male	733	943	117.5	34.1
FA040	14	Male	505	1345	119.5	44.6
FA041	10	Male	593	957	48.5	16.0
FA042	10	Female	706	706	N/A	46.4
FA043	13	Female	747	875	98.5	28.0
FA044	6	Male	713	875	111	25.7
FA045	12	Male	818	818	78	22.2
FA046	18	Female	489	1207	140	65.1
FA047	17	Male	589	589	N/A	52.2
FA048	14	Male	853	853	N/A	40.9

FA049	10	Male	779	932	70	18.0
FA050	7	Male	998	998	96.5	23.2
FA051	4	Female	556	733	66	16.4
FA052	16	Female	690	690	109.7	57.4
FA053	11	Male	647	915	N/A	26.9
FA054	32	Female	674	803	84	48.6
FA055	13	Male	558	784	101.5	47.4
FA056	16	Male	630	850	55.5	25.7
FA057	28	Male	383	942	69.5	N/A
FA058	17	Male	1050	1050	62.5	27.8
FA059	6	Male	1015	1015	125	26.9
FA060	21	Male	527	1058	79	37.1
Mean ($\bar{x}$)	15.4	Female=22	627.5	863.7	91.1	35.5
Standard deviation (σ)	7.7	Male =37	193.1	197	26.5	12.2
Range	3-34		126-1099	320-1345	37.5-140	15.5-65.1

4.5.2 Assessment

Swallowing-related QOL was assessed using the Swal-QOL (McHorney et al., 2000); a validated tool consisting of 44 items covering 10 quality of life domains pertaining to dysphagia, including; Burden, Eating Duration, Eating Desire, Food Selection, Communication, Fear, Mental Health, Social, Fatigue, and Sleep. The Swal-QOL includes a symptom frequency scale consisting of 14 commonly reported signs of dysphagia. Each item is scored on a scale from one to five, where 5 = optimal, and 1 = maximal impairment. Scores for each Swal-QOL domain were calculated via the following equation: *((participant's raw score - minimal possible raw score) / possible raw score range) * 100*

A total SWAL-QOL score is derived by summing each domain score and dividing by 11 giving a total SWAL-QOL score that ranges between 0 and 100 (worst–best).

4.5.3 Statistical analysis

Describing swallowing-related QOL

Descriptive statistics were used to explain the scores for each Swal-QOL item (44), as well as each Swal-QOL accumulated domain score, and the total accumulated Swal-QOL score. Each Swal-QOL item was analysed as a dependent variable to determine the degree of impairment for each item.

Investigating the relationships between swallowing-related QOL and FRDA

Spearman's rho (ρ) correlations were used to investigate the relationships between Swal-QOL item scores and FRDA clinical parameters (age at symptom onset and assessment, disease duration, *FXN* intron 1 GAA repeat sizes and FARS score).

Swallowing-QOL in FRDA versus healthy controls

Comparisons between the FRDA and HC groups were calculated using Mann-Whitney U tests. Effect size was interpreted as 0.1=small effect, 0.3=medium effect, and 0.5=large effect (Cohen, 1988).

Software

Statistical analysis was performed using SPSS Statistical Software Version 22.0 (IBM®, Armonk, New York, United States of America).

4.6 Results

4.6.1 Burden

The mean scores for the FRDA group were significantly lower than that of the HC group for both items (item 1: FRDA $\bar{x}$ 4.31 σ 0.97, HC $\bar{x}$ 4.95 σ 0.29, $p<0.01$; item 2: FRDA $\bar{x}$ 4.51 σ 0.75, HC $\bar{x}$ 0.93 σ 0.41 $p<0.01$). Twenty six of the 59 (44.1%) participants in the FRDA group reported dealing with their swallowing problem was difficult, compared to 2/60 (3.3%) of the HC group. Twenty-two of the 59 participants (37.3%) in the FRDA group reported that dysphagia is a major distraction in their life, compared to 2/60 (3.3%) in the HC group. The total Burden domain score was lower in the FRDA group compared to the HC group (FRDA $\bar{x}$ 87.17 σ 19.90, HC $\bar{x}$ 100 σ 0.00, U=870.00, z=-6.28, p=0.00, r=-0.81) (Table 4.2; Figure 4.1).

4.6.2 Eating Desire

Seventeen of the 59 (28.8%) of the FRDA group recorded a positive response to Most days, I don't care if I eat or not, compared to six of the 60 (10.0%) of the HC group. For the second item, 17/59 (28.8%) individuals with FRDA reported they are rarely hungry anymore compared to 9/60 (15.00%) of the HC group. For item 3, 9/59 (15.5%) individuals with FRDA reported less eating enjoyment, compared with 4/60 (6.7%) of the HC group. The overall domain score was significantly lower in the FRDA group compared to the HC group (FRDA $\bar{x}$ 89.55 σ 16.78, HC $\bar{x}$ 95.28 σ 13.19, U=1369.50, z=-2.65, p=0.01, r=-0.34) (Table 4.2; Figure 4.1).

4.6.3 Eating Duration

Forty-five of the 59 participants 45/59 (76.27%) reported eating meals takes longer than other people, compared to 10/60 (16.7%) of the HC group. For item 2, 33/59 (55.6%) individuals with FRDA reported it took forever to eat a meal, compared to 3/60 (5.0%) of the HC group. The overall domain score was significant different (FRDA $\bar{x}$ 64.19 σ 30.39, HC $\bar{x}$ 89.39 σ 12.87, U=873.00, z=-4.94, p=0.00, r=-0.64) (Table 4.2; Figure 4.1).

4.6.4 Symptom Frequency

All of the items in the frequency symptom scale were significantly different between the FRDA and HC groups ($p<0.01$). The most frequently experienced symptom by individuals with FRDA was coughing, reported by 51/59 (86.44%) participants compared to 27/60 (45.0%) participants in the HC group. Throat clearing was the second most frequently reported symptom by the FRDA group (45/59, 76.27%), compared to the HC group (26/60, 43.3%). The dysphagia symptom experienced the least by the FRDA group was food or liquid coming out of the nose (16/59 (27.12%), compared to 2/60 (3.3%) of the HC group). The overall mean of the FRDA group was lower than the HC group (FRDA $\bar{x}$77.33 σ 16.06 HC $\bar{x}$ 94.43 σ 7.47, U=566.00, z=-6.46, p=0.00, r=-0.84) (Table 4.2; Figure 4.1).

4.6.5 Food Selection

Nineteen of the 59 (32.2%) participants with FRDA reported figuring out what they can and can't eat is problematic, compared to 2/60 (3.3%) of the HC group. For item 2, 14/59 (23.7%) participants with FRDA reported difficultly finding foods they like and can eat, compared to 3/60 (5.0%) of the HC group. The overall domain score was also significantly different (FRDA $\bar{x}$ 89.62σ 17.39, HC $\bar{x}$ 98.13 σ 9.15, U=1264.00, z=-3.91, p=0.00, r=-0.51) (Table 4.2; Figure 4.1).

4.6.6 Communication

Forty of the 59 (67.8%) individuals with FRDA reported difficulty being understood (item 1), compared to 2/60 (3.3%) in the HC group. Thirty-seven of 59 (62.7%) of the FRDA group reported difficulty speaking clearly, compared to 1/60 (1.7%) of the HC group. The overall domain score was also significant different between the two groups (FRDA $\bar{x}$ 74.15 σ 21.76, HC $\bar{x}$ 99.38 σ 3.58, U=571.00, z=-7.42, p=0.00, r=-0.97) (Table 4.2; Figure 4.1).

4.6.7 Fear

Twenty-nine of 59 (49.15%) individuals with FRDA reported a fear of choking with food, compared to 4/60 (6.7%) in the HC group. Fourteen of the 59 (23.73%) individuals with FRDA reported fear of getting pneumonia, compared to 3/60 (5.0%) of the HC group. For item 3, 34 of the 59 (57.63) in the FRDA group reported fear of choking when drinking liquids, compared to 4/60 (6.7%) of the HC group. More individuals in the FRDA group reported fear of choking (35/59, 61.0%), compared to the HC group (3/60, 5.0%). The overall domain score was significantly different between the two groups (FRDA $\bar{x}$ 78.39 σ 20.48, HC $\bar{x}$ 98.23 σ 6.10, U=637.50, z=-6.75, p=0.00, r=-0.88) (Table 4.2; Figure 4.1).

4.6.8 Mental Health

For item 1, 15/ 59 (25.42%) of the FRDA group reported their swallowing problem was depressing for them, compared to 1/60 (1.7%) of the HC group. For item 2, 31/59 (52.5%) of the FRDA group reported annoyance with having to be so careful when eating or drinking, compared to 1/60 (1.7%) of the HC group. Nineteen of 59 (32.2%) of the FRDA group reported feeling discouraged by their swallowing problem, compared to 1/60 (1.7%) in the HC group. Twenty-three of the 59 (38.98%) of the FRDA group reported frustration due to their swallowing problem, compared to 2/60 (3.3%) of the HC group. For the final item, 18/59 (30.51%) individuals with FRDA reported getting impatient dealing with their swallowing problem, compared to 1/60 (1.7%) of the HC group. The overall domain score was also significantly different between the two groups (FRDA $\bar{x}$ 22.15 σ 3.69, HC $\bar{x}$ 24.90 σ 0.66, $p<0.01$) (Table 4.2; Figure 4.1).

4.6.9 Social

Fourteen of the 59 (23.7%) participants in the FRDA group reported they do not go out to eat because of their swallowing problem (item 1) compared to 1/60 (1.7%) in the HC group. Twelve of the 59 (20.3%) participants in the FRDA group reported their swallowing problem makes it hard to have a social life, compared to 2/60 (3.3%) of the HC group. Twelve of the

59 (20.3%) participants in the FRDA group reported their usual work or leisure activities have changed because of their swallowing problem, compared to 1/60 (1.7%) of the HC group. For item 4, 11/59 in the FRDA group reported social gatherings were not enjoyable due to their swallowing problem, compared to 1/60 (1.7%) of the HC group, whilst 10/59 in the FRDA group and 1/60 (1.7%) in the HC group reported a change in their role with family and friends because of their swallowing problem. The overall domain score was also significant different between the two groups (FRDA $\bar{x}$ 92.46 σ 15.74, HC $\bar{x}$ 99.50 σ 3.28, U=1342.50, z=-4.24, p=0.00, r=-0.55) (Table 4.2; Figure 4.1).

4.6.10 Fatigue

Thirty-nine of 59 (66.1%) of the FRDA group, and 9/60 (15.0%) of the HC group reported feeling weak (item 1). Tiredness (item 2) was reported by 49/59 (83.1%) of the FRDA group and 44/60 (73.3%) of the HC group. Exhaustion (item 3) was reported by 46/59 (78.0%) of the FRDA group and 32/60 (53.3%) of the HC group. The overall domain score was also significant different between the two groups (FRDA $\bar{x}$ 59.75 σ 27.82, HC $\bar{x}$ 80.83 σ 17.31, U=980.50, z=-4.24, p=0.00, r=-0.55) (Table 4.2; Figure 4.1).

4.6.11 Sleep

Thirty-nine of the 59 (66.1%) individuals with FRDA and 32/60 (53.3%) of the HC group reported trouble falling asleep, whilst 50/59 of the FRDA group and 25/60 (41.7%) of the HC group reported trouble staying asleep. The overall domain score was also significantly different between the two groups (FRDA $\bar{x}$ 71.19 σ 27.68, HC $\bar{x}$ 83.75 σ 18.31, U=1334.50, z=-2.38, p=0.02, r=-0.31) (Table 4.2; Figure 4.1).

4.6.12 Total Swal-QOL score

Overall swallowing-related QOL (total Swal-QOL score) was significantly reduced in the FRDA group compared to the HC group (FRDA $\bar{x}$ 78.87 σ 15.03, HC $\bar{x}$ 94.27σ 5.82, U=559.00, z=-6.44, p=0.00, r=-0.84) (Table 4.2; Figure 4.1).

4.7 Relationship between FRDA clinical parameters and swallowing-related QOL

A trend emerged relating disease duration and severity (FARS score) with reduced swallowing-related QOL. Total Swal-QOL score negatively correlated with FARS (ρ = -0.43, $p>0.01$) and disease duration (ρ=-0.44, $p<0.05$) and disease duration (ρ=-0.37, $p<0.05$). FARS negatively correlated with Burden (ρ = -0.34, $p<0.05$), Symptom Frequency (ρ = -0.37, $p<0.01$), Food Selection (ρ = -0.31, $p<0.05$), Communication (ρ = -0.45, $p<0.01$), Fear (ρ = -

0.43, $p<0.01$), and Mental Health ($\rho = -0.32$, $p<0.05$). Disease duration negatively correlated with Burden ($\rho = -0.38$, $p<0.05$), Eating Duration ($\rho = -0.34$, $p<0.5$), Food Selection ($\rho = -0.33$, $p<0.05$), Communication ($\rho = -0.51$, $p<0.01$), and Mental Health ($\rho = -0.35$, $p<0.05$). No correlations were observed between swallowing-related QOL and GAA1 and GAA2 lengths (Table 4.3).

Figure 4-1 Swal-QOL percentage scores – FRDA versus HC groups

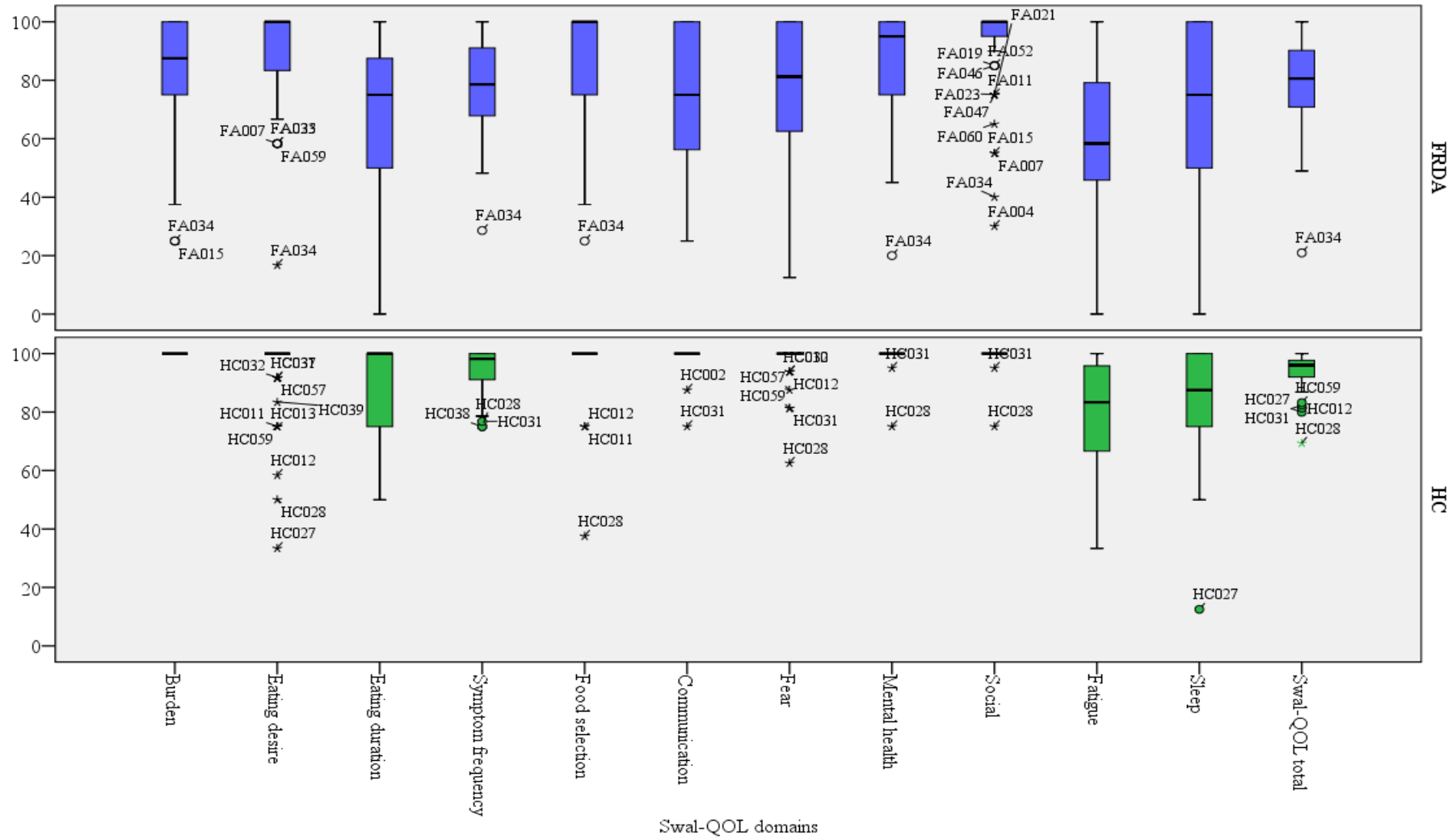


Table 4-2 Swallowing-related QOL in individuals with FRDA and healthy controls

	FRDA (n=59)		HC (n=60)		Mann-Whitney U test
SWAL-QOL Domain	Mean	SD	Mean	SD	
Burden	85.17	19.90	100.00	0.00	U=870.00, z=-6.28, p=0.00, r=-0.81
Eating Duration	64.19	30.39	89.38	12.87	U=873.00, z=-4.94, p=0.00, r=-0.64
Eating Desire	89.55	16.78	95.28	13.19	U=1369.50, z=-2.65, p=0.01, r=-0.34
Symptom Frequency	77.33	16.06	94.43	7.47	U=566.00, z=-6.46, p=0.00, r=-0.84
Food Selection	89.62	17.39	98.13	9.15	U=1264.00, z=-3.91, p=0.00, r=-0.51
Communication	74.15	21.76	99.38	3.58	U=571.00, z=-7.42, p=0.00, r=-0.97
Fear	78.39	20.48	98.23	6.10	U=637.50, z=-6.75, p=0.00, r=-0.88
Mental Health	85.76	18.45	99.50	3.28	U= 856.5, z=-6.09, p=0.00, r=-0.79
Social	92.46	15.74	99.50	3.28	U=1342.50, z=-4.24, p=0.00, r=-0.55
Fatigue	59.75	27.82	80.83	17.31	U=980.50, z=-4.24, p=0.00, r=-0.55
Sleep	71.19	27.68	83.75	18.31	U=1334.50, z=-2.38, p=0.02, r=-0.31
Total	78.87	15.03	94.27	5.82	U=559.00, z=-6.44, p=0.00, r=-0.84

Table 4-3 Relationships between swallowing-related QOL and FRDA clinical parameters

Swal-QOL items		GAA1	GAA2	FARS	Age at onset	Age at assessment	Disease duration
Burden	Dealing with my swallowing problem is very difficult	-0.03	-0.14	-0.34*	0.08	-0.18	-0.40*
	My swallowing problem is a major distraction in my life	-0.11	0.00	-0.30*	0.24	-0.17	-0.31
	Total domain score	-0.05	-0.09	-0.34*	0.15	-0.21	-0.38*
Eating Desire	Most days, I don't care if I eat or not	0.00	0.23	-0.04	0.07	0.08	0.02
	I'm rarely hungry anymore	0.03	-0.07	-0.17	-0.02	-0.07	-0.01
	I don't enjoy eating anymore	0.07	-0.03	-0.18	0.04	-0.17	-0.14
	Total domain score	-0.01	0.06	-0.14	0.05	-0.03	-0.07
Eating Duration	It takes me longer to eat than other people	0.00	-0.11	-0.23	-0.01	-0.25	-0.36*
	It takes me forever to eat a meal	-0.04	-0.07	-0.28*	0.16	0.00	-0.30
	Total domain score	-0.01	-0.09	-0.28	0.07	-0.15	-0.34*
Symptom Frequency	Coughing	0.06	-0.04	-0.34*	0.09	-0.19	-0.26
	Choking when you eat food	-0.05	-0.03	-0.21	0.03	-0.13	-0.13
	Choking when you take liquids	-0.23	-0.04	-0.23	0.04	-0.15	-0.15

	Having thick saliva or phlegm	0.01	-0.05	-0.29*	0.12	-0.24	-0.36*
	Gagging	-0.04	-0.06	-0.32*	0.09	-0.33*	-0.39*
	Drooling	0.09	0.06	0.03	0.13	0.08	-0.06
	Problems chewing	-0.12	0.08	-0.31*	0.25	-0.06	-0.28
	Having excess saliva or phlegm	-0.02	-0.10	-0.25	0.17	-0.09	-0.22
	Having to clear your throat	0.11	0.00	-0.40**	-0.03	-0.43**	-0.40*
	Food sticking in your throat	-0.07	-0.05	-0.28	0.20	-0.11	-0.23
	Food sticking in the mouth	0.02	0.00	-0.35*	0.28*	0.00	-0.16
	Food or liquid dribbling out of your mouth	-0.08	-0.01	-0.15	0.25	-0.03	-0.14
	Food or liquid coming out of your nose	0.05	0.14	-0.09	0.01	-0.15	-0.18
	Coughing food or liquid out of your mouth when it gets stuck	-0.05	-0.02	-0.37**	0.10	-0.16	-0.15
	Total domain score	-0.06	-0.02	-0.37**	0.18	-0.20	-0.30
Food Selection	Figuring out what I can and can't eat is a problem for me	0.10	-0.09	-0.32*	0.01	-0.21	-0.30
	It is difficult to find foods that I both like and can eat	0.03	0.01	-0.22	0.02	-0.12	-0.22
	Total domain score	0.05	-0.07	-0.31*	0.03	-0.22	-0.33*

Communication	People have a hard time understanding me	0.04	0.06	-0.41**	0.19	-0.22	-0.44**
	It's been difficult for me to speak clearly	0.00	-0.07	-0.42**	0.19	-0.26*	-0.48**
	Total domain score	0.00	-0.02	-0.45**	0.20	-0.26*	-0.51**
Fear	I fear I may start shocking when I eat food	-0.11	0.09	-0.20	0.00	-0.26*	-0.18
	I worry about getting pneumonia	0.10	0.05	-0.30*	0.10	-0.22	-0.28
	I am afraid of choking when I drink liquids	-0.06	0.07	-0.49**	0.15	-0.23	-0.28
	I never know when I am going to choke	0.00	-0.09	-0.36*	0.00	-0.20	-0.23
	Total domain score	-0.04	0.01	-0.43**	0.08	-0.29*	-0.29
Mental Health	My swallowing problem depresses me	0.06	0.09	-0.20	0.18	-0.15	-0.29
	Having to be so careful when I eat or drink annoys me	0.05	-0.08	-0.29*	0.03	-0.21	-0.34*
	I've been discouraged by my swallowing problem	-0.02	-0.06	-0.34*	0.19	-0.22	-0.43**
	My swallowing problem frustrates me	-0.09	-0.07	-0.19	0.08	-0.22	-0.27
	I get impatient dealing with my swallowing problem	-0.09	-0.09	-0.28*	0.29*	0.01	-0.22
	Total domain score	-0.02	-0.060	-0.32*	0.15	-0.19	-0.35*
Social	I do not go out because of my swallowing problem	0.16	0.19	-0.18	0.09	-0.15	-0.11

	My swallowing problem makes it hard to have a social life	0.21	0.09	-0.14	0.08	-0.04	-0.11
	My usual work or leisure activities have changed because of my swallowing problem	0.24	0.00	-0.29*	0.06	-0.16	-0.30
	Social gatherings (like holidays or get-togethers) are not enjoyable because of my swallowing problem	0.20	0.15	-0.10	0.03	-0.10	-0.13
	Total domain score	0.19	0.13	-0.20	0.04	-0.18	-0.17
	My role with family and friends gas changed because of my swallowing problem	0.23	0.14	-0.15	0.05	-0.12	-0.18
Fatigue	Feel weak?	0.11	0.06	-0.12	0.13	0.10	0.13
	Feel tired?	-0.02	0.01	-0.21	0.16	0.03	0.04
	Feel exhausted?	-0.05	-0.06	-0.22	0.20	0.06	0.00
	Total domain score	0.00	-0.01	-0.19	0.19	0.08	0.07
Sleep	Have trouble falling asleep?	0.04	0.00	-0.17	0.15	0.07	0.00
	Have trouble staying asleep?	-0.01	0.01	-0.21	0.04	-0.24	-0.27
	Total domain score	-0.00	0.00	-0.18	0.11	-0.07	-0.13
Total		-0.04	-0.08	-0.44**	0.19	-0.21	-0.37*

** Significant at p<0.01 (2-tailed), * significant at p<0.05 (2-tailed)

4.8 Discussion

Individuals with FRDA experience reduced QOL related to swallowing impairment compared to a healthy population, confirming the primary hypothesis. Correlations were revealed between swallowing-related QOL and disease severity and duration, supporting the second hypothesis. These results bring to the forefront the need to consider the psychosocial impact of dysphagia in the management of individuals with FRDA.

4.8.1 Swallowing-related QOL in individuals with FRDA

Results of this research demonstrate the significant burden dysphagia places on individuals with FRDA. Participants identified swallowing impairment as challenging to deal with and a major distraction in their lives. Additionally, individuals with FRDA reported difficulty finding foods they can both eat and enjoy, and report extended mealtimes secondary to swallowing impairment. Mealtimes are likely to be prolonged by upper limb dysfunction manifesting in difficulty self-feeding. Difficulty self-feeding may in turn impact on the desire to eat, which was significantly reduced in the FRDA group compared to HC group. Difficulty feeding may contribute to feelings of fatigue or sleepiness, which were more apparent in the FRDA group. The dysphagia-related burden and lengthy mealtimes experienced by individuals with FRDA may be related to the implementation of safe swallowing strategies, such as using a '*chin tuck'* technique, or preparing softer foods (Garcia & Chambers Iv, 2010b; Germain et al., 2006; Nagaya et al., 2004). These compensatory swallowing strategies are commonly recommended to individuals with FRDA (Corben et al., 2014; Vogel et al., 2014).

Individuals with FRDA report a change in their role within their family and social groups, as well as reduced participation in social events and gatherings. Furthermore, individuals with FRDA also avoid eating and drinking in public. These results are consistent with previous research where a relationship between dysphagia and social restriction and isolation has been reported (Carneiro et al., 2014; Ekberg et al., 2002; Vesey, 2013). Individuals with dysphagia often find eating and drinking less enjoyable and experience significant anxiety and panic at mealtimes (as reported in a cohort of 360 nursing home residents) (Ekberg et al., 2002). Furthermore, individuals with dysphagia avoided eating with others (Chow et al., 2004; Ekberg et al., 2002). Dysphagia is also associated with embarrassment and reduced self-esteem and confidence (Farri et al., 2007; Nguyen et al., 2005). Such factors can impact on social relationships and lead to social isolation (Farri et al., 2007). In FRDA, issues with

communication (Folker et al., 2010), including difficulty being understood and speaking clearly may also contribute to social isolation.

Dysphagia can affect the mental health of individuals with FRDA. In the present study, individuals with FRDA reported significant frustration and depression related to swallowing dysfunction compared to the HC group. Inability to participate in social gatherings, reluctance to leave home, and the burden associated with having a swallowing problem experienced by individuals with FRDA is also likely to contribute to a reduction in mental health overall. The fact that individuals with FRDA report an ongoing desire to eat, in spite of swallowing impairment, is likely to exacerbate feelings of frustration toward eating and drinking.

4.8.2 Progression of swallowing-related QOL in FRDA

This single time point study does not allow for longitudinal analysis of swallowing-related QOL in FRDA. However, significant positive correlations revealed between Swal-QOL scores and disease duration and severity suggest that swallowing-related QOL worsens in line with disease progression. This result was unsurprising given the relationship between disease severity and physical QOL, and disease duration and mental QOL in individuals with FRDA (Wilson et al., 2007). Mapping the impact of dysphagia on QOL over time in individuals with FRDA would be useful to determine if this pattern is maintained.

4.8.3 Clinical implications of this research

The multidimensional effect of dysphagia on the wellbeing of individuals with FRDA is reflective of the condition. FRDA manifests in widespread neuropathology inclusive of the neural tracts involved in speech and swallowing. Thus, it is unsurprising that dysphagia symptoms were reported by individuals with FRDA at a greater rate than healthy controls. Auxiliary complications of FRDA, including scoliosis which may impinge feeding posture, and limb dysfunction making feeding difficulty, are likely to further affect swallowing function. A finding of reduced QOL secondary to dysphagia is not exclusive to the FRDA population. Leow and colleagues (2010) found that individuals with Parkinson disease (PD) experienced a significant reduction in QOL as a consequence of dysphagia compared to healthy controls, with similar results found in a cohort of individuals with amyotrophic lateral sclerosis (Paris et al., 2013). Swallowing-related QOL has also been previously reported to relate to disease severity in idiopathic PD (Plowman-Prine et al., 2009). These results necessitate close monitoring of dysphagia commencing form the onset of neurodegenerative

disease, with the expectation that swallowing function may worsen as the disease progresses requiring more invasive intervention.

4.8.4 Limitations of the present study

No steps were taken to control for depression not related to dysphagia in this study. Dysphagia is reported to be independently associated with depression and anxiety, and other affective disorders in the general population (Eslick & Talley, 2008). Anxiety and depression are also prevalent in individuals presenting with dysphagia following treatment for head and neck cancer, and worsen in line with dysphagia severity (Nguyen et al., 2005). Dysphagia is also a significant risk factor for depression and negative psychosocial manifestations in nursing home residents (Chow et al., 2004; Ekberg et al., 2002). In a study of 360 nursing home residents with complaints of dysphagia, 84% reported eating should be an enjoyable experience, however only 45% reported eating to be enjoyable (difference of 39%). Furthermore, 41% of the cohort reported feeling panicked at mealtimes, while 36% avoided eating and drinking with others due to dysphagia (Ekberg et al., 2002). The relationship between dysphagia and depression is also widely acknowledged in various neurodegenerative populations, such as multiple sclerosis (MS) (Bretan, Henry, & Kerr-Correa, 1995), ALS (Hillemacher et al., 2004), and PD (Mottram et al., 2011). In a study of five individuals with MS with dysphagia, four were found to have anxiety and one was found to have depression. Dysphagia symptoms were reported to improve following an informed discussion regarding normal swallowing and the role of emotions (Bretan et al., 1995). Han and colleagues (2011) evaluated the depressive states of 127 individuals with PD, with results suggesting a strong link between depression and dysphagia. Hillemacher and colleagues (2004) noted a relationship between bulbar symptoms and depression in a sample of 41 individuals with ALS. This evidence highlights the insidious nature of dysphagia and that its consequences extend far beyond that of physical ill-health. The mental and psychological state of a patient should always be considered when evaluating swallowing function.

4.8.5 Clinical implications of this study

Swallowing assessment and management has historically focussed on the physiological impairment rather than the psychosocial limitations imposed and associated activity and participation restrictions. This study highlights the multifaceted psychosocial implications of FRDA-related dysphagia which must be considered in the overall management of the condition. FRDA-related dysphagia should be collaboratively managed by the neurologist,

speech pathologist, and a mental health practitioner. Further, rehabilitation goals should focus on swallowing education, maximising social exposure, and reducing the burden experienced by individuals with FRDA-related dysphagia, and therefore reduce the risk of mental health issues.

4.9 Summary

Dysphagia detrimentally affects the lives of individuals with FRDA. Individuals with the disease experience significant burden, social restriction, and mental health implications as a result of swallowing impairment. Most pertinently, individuals with FRDA perceive their role in their familiar and social groups differently as a result of their dysphagia. These results should be taken into account when managing an individual with FRDA and associated dysphagia clinically.

Chapter 5 Study 2 – Clinical bedside examination of oromotor function and swallowing in FRDA using a standardised assessment

5.1 Research questions

Swallowing difficulties arise when oromotor function is disturbed (McCullough et al., 2005; Yoshida et al., 2006). An assessment of oromotor function is a crucial component of the dysphagia assessment battery (McCullough & Martino, 2013). The aim of this study is to explore and describe oromotor function in individuals with FRDA using a standardised assessment of sensorimotor function of the speech and swallowing mechanism; the Frenchay Dysarthria Assessment (second edition) (FDA-2) (Enderby, 2011). Completion of this study will address the following research questions:

1. What are the characteristics (including severity) of oromotor dysfunction in individuals with FRDA?
2. What is the relationship, if any, between oromotor dysfunction and FRDA clinical parameters (age at onset and assessment, disease duration, GAA1 and GAA2 lengths, and disease severity as measured by the FARS)?

5.2 Aims and hypotheses

Aim 1 - To characterise oromotor function in individuals with FRDA.

Hypothesis - It is hypothesised that individuals with FRDA present with deficits across all FDA-2 domains.

Aim 2 - To determine the relationships between oromotor impairment and clinical disease markers of FRDA (age at onset and assessment, disease duration, GAA1 and GAA2 lengths, and disease severity as measured by the FARS).

Hypothesis - FRDA-related oromotor deficits will correlate with measures of disease severity and duration.

5.3 Rationale

A thorough examination of oromotor function is an important step in the dysphagia assessment battery (McCullough & Martino, 2013). Oromotor impairment is expected in FRDA (Eigentler et al., 2012). To date, the relationships between oromotor dysfunction and dysphagia in individuals with FRDA have not been determined. This study will quantify oromotor deficits in FRDA using a standardised measure of oromotor function, the FDA-2.

The FDA-2 is a reliable measure of oromotor function and correlated with measures of disease (Eigentler et al., 2012).

5.4 Background

Oromotor impairment is expected in FRDA and the majority of research has focussed on the resulting change in speech function. Perceptual and acoustic studies report imprecise consonant production, limited pitch variation, disturbed loudness, short phrase length, disturbed nasality, and equal and excess stress (Folker et al., 2010; Joanette & Dudley, 1980; Poole et al., 2015), all demonstrative of globally disrupted oromotor processes.

Eigentler and colleagues (2012) investigated the oral kinematics of 15 individuals with FRDA using the first edition of the FDA and reported impairment across multiple domains. Laryngeal (vocal) function was most severely affected, followed by reflexive function (including cough, swallowing, and dribble/drool), palatal function, and lingual function. Respiratory function was the least affected domain (Eigentler et al., 2012). Kinematic analysis has revealed underlying spatial impairment rather than pure slowed movement execution affecting lingual function in individuals with FRDA. Folker and colleagues (2011a) investigated lingual kinematics in individuals four with FRDA using electromagnetic articulography (EMA) during six repetitions of the tongue tip sentence *Tess told Dan to stay fit* and the tongue back sentence *Karl got a croaking frog.* Results revealed longer movement durations and increased movement distance. Furthermore, slower maximum velocities were recorded during the approach phase (movement of the tongue tip to the hard palate) of consonant production. The release phase of consonant production was comparable to a group of controls. Folker and colleagues (2011b) extended this study by analysing lingual movements during specific consonant (/t/ and /k/) productions produced in sentences and rapid syllable repetition in four individuals with FRDA. The prominent finding was prolonged consonant phase durations on alveolar (/t/) and velar (/k/) consonant production – a documented feature of ataxic dysarthria. Interestingly, participants in this study demonstrated increased velocity of movement, which contradicts results of acoustic studies which have consistently reports slower articulatory movement in individuals with FRDA (Ackermann & Hertrich, 1993; Gentil, 1990). The EMA data collected by Folker and colleagues (2011b) shows articulatory disturbance in FRDA characterised by prolonged consonant phase duration is related to great articulatory distance rather than slowed movement of execution.

Studies of speech function in individuals with FRDA report correlations between dysarthria and disease duration and severity (FARS) (Folker et al., 2010), suggesting speech function worsens over time in this populations. There is evidence suggesting that oromotor impairment is correlated with GAA1 length (Eigentler et al., 2012) however these data have not been replicated.

5.5 Methods

5.5.1 Participants

Thirty five of the 59 individuals who participated in Study 1 - Swallowing-related quality of life in individuals with Friedreich ataxia (59.32%) were assessed using the FDA-2 assessment (Table 5.1). Of the remaining 24 individuals, 12 did not participate in further assessment due to logistical reasons (such as transport issues), 10 declined further assessment, and one participant did not present with signs of dysphagia on Swal-QOL or case history, therefore did not meet inclusion criteria for undergoing assessment using FDA-2.

Table 5-1 Demographic and clinical characteristics of participants (FDA-2) (n=35)

ID	Age at disease onset	Gender	GAA1	GAA2	FARS score	Age
FA001	13	female	706	811	106.5	43.3
FA002	5	male	1099	1099	N/A	39.6
FA003	24	male	682	1041	96	45.5
FA005	14	male	720	720	66	29.7
FA006	15	male	720	720	68	29.7
FA007	3	male	645	771	127.5	38.0
FA009	14	male	471	590	74.5	24.3
FA010	14	male	552	552	71.5	29.8
FA011	11	female	444	526	70.5	22.2
FA012	14	male	650	900	129	44.6
FA013	18	female	447	967	102	31.4
FA015	8	female	642	1132	136	39.3
FA016	28	male	606	986	102.5	53.9
FA017	20	female	646	1293	115.7	49.6
FA021	7	male	780	980	138.5	51.0
FA023	10	male	659	822	109.5	25.8
FA024	12	male	850	850	N/A	49.3
FA027	26	male	560	989	N/A	51.0
FA028	19	male	476	545	76.5	37.4
FA029	14	female	833	835	95.5	31.7
FA030	6	male	815	856	N/A	15.5
FA032	14	male	569	884	77	23.6
FA034	21	female	462	462	84.5	38.8

FA035	14	female	727	727	90.5	33.6
FA036	30	female	414	590	63.5	34.7
FA037	3	male	800	800	109.5	21.3
FA039	8	male	733	943	117.5	33.7
FA042	10	female	706	706	N/A	46.4
FA047	17	male	589	589	N/A	52.2
FA048	14	male	853	853	N/A	40.9
FA049	10	male	779	932	70	17.5
FA052	16	female	690	690	109.7	57.4
FA054	32	female	674	803	84	48.6
FA055	13	male	558	784	101.5	47.4
FA056	16	male	630	850	55.5	25.7
Mean ($\bar{x}$)	14.66		662.49	817.09	94.60	37.27
Standard deviation (σ)	7.11		143.70	186.11	23.47	11.15
Range	3-32		414-1099	462-1293	55.5-138.5	17.5-64.8

5.5.2 Assessment

Oromotor function was assessed using the FDA-2 (Enderby, 2011) which consists of 26 items across seven oromotor domains, including: *Reflexes (*ratings for cough, swallow, and dribble/drool), *Respiration* (ratings for rest and in speech), *Lips (*ratings for at rest, spread, seal, during alternate movement, and in speech), *Laryngeal* (ratings for time, pitch, volume, and in speech), *Tongue* (ratings for rest, protrusion, elevation, lateral, alternate, and in speech), and *Intelligibility* (*r*atings for words, sentences, and conversation). For each FDA-2 domain the participant is observed at rest and directed a task to complete targeted to the appropriate functional area. Results are marked on an ordinal scale with a performance descriptor provided for each subtest. The rating scale consists of 9 points, ranging from '*a'* to '*e'* (with half scores possible*)*, where '*a'* denotes normal function, and '*e'* denotes maximal impairment. For this study scoring was adapted by replacing alphabetic coding with numeric scoring. Each item was scored on a 9 point severity scale (1 to 9), in which 1 corresponds to normal function and 9 indicates no function. Therefore, scores on the FDA-2 increase with impairment severity. For each of the seven distinct FDA-2 items, the arithmetic $\bar{x}$ from the tasks was calculated. For ease of reporting impairment severity, individuals who scored 1 as '*normal*', 2 to 4 as '*mildly impaired*', 5 to 6 as '*moderately impaired*', 7 to 8 as '*severely impaired*', and 9 as '*maximally impaired'*.

The FDA-2 has strong reliability and validity (Enderby, 2011; Enderby & Palmer, 2008) and provides comprehensive assessment of the essential elements of an oromotor assessment as defined by McCullough and Martino (2013). The FDA-2 can be time-consuming to administer and relies heavily on the assessor's own interpretation (Enderby, 2011).

5.5.3 Statistical analysis

Describing oromotor function in FRDA

Descriptive statistics were used to evaluate FDA-2 results and outline impairments observed on assessment.

Relationships between oromotor function and FRDA

Spearman's rho (ρ) correlations were used to investigate the relationship between oromotor function and FRDA (including GAA repeat length, disease severity and disease duration).

Reliability

Each FDA-2 assessment was conducted by the author; a qualified Speech Pathologist. The assessments were filmed using a handheld camera and recordings were used for repeat ratings to establish intra and interrater reliability. A secondary rater (also a qualified Speech Pathologist) rated the videos to establish inter-rater reliability. Intra and inter-rater reliability was determined using Cohen's Kappa agreement, with values as stipulated by Viera and Garrett (2005): < 0 - *Less than chance agreement*; 0.01 to 0.20 - *Slight agreement*; 0.21 to 0.40 - *Fair agreement*; 0.41 to 0.60 - *Moderate agreement*; 0.61 to 0.80 - *Substantial agreement*; 0.81 to 0.99 - *Almost perfect agreement* (Viera & Garrett, 2005). Statistical analysis was performed using SPSS Statistical Software Version 22.0 (SPSS®IBM Corporation, Armonk, New York, USA).

5.6 Results

5.6.1 Reliability

Intrarater reliability

Repeat ratings were conducted on average 408 (+/- 153.3 days) days after the initial rating. Overall intrarater agreement was Kappa 0.717 (p = 0.000), indicating moderate agreement. The level of agreement for each item ranged from fair (> 0.21) to almost perfect agreement (0.81-0.99) (Viera & Garrett, 2005). The lowest level of agreement (Kappa 0.276, p = 0.037) was observed for *Lips – spread* indicating only fair agreement however this was not statistically significant. The highest level of agreement was *Reflex – swallow* (Kappa 0.913, p=0.000) suggesting almost perfect agreement.

Inter-rater reliability

The second rater was trained by the author and rated 24 FDA-2 videos. Overall inter-rater reliability was Kappa 0.592 (p=0.000), indicating moderate agreement. Sub-item analysis revealed *fair* (*Lips – seal*: Kappa 0.234, p=0.039) to *almost perfect* (*Reflexes – cough*: Kappa 0.851, p=0.000) agreement (Table 5.2).

Table 5-2 Rater agreement - FDA-2

FDA-2 domains	Sub items	Interrater agreement	Intrarater agreement
Reflexes	Cough	0.85**	0.89**
	Swallow	0.77**	0.91**
	Dribble/Drool	0.61**	0.72**
Respiration	Rest	0.47**	0.67**
	In Speech	0.51**	0.62**
Lips	Rest	0.78**	0.87**
	Spread	0.27**	0.28**
	Seal	0.23**	0.67**
	Alternate	0.37**	0.56**
	In Speech	0.70**	0.73**
Palate	Fluids	0.36**	0.72**
	Maintenance	0.65**	0.84**
	Speech	0.42**	0.55**
Laryngeal	Time	0.70**	0.83**
	Pitch	0.73**	0.76**
	Volume	0.53**	0.63**
	In speech	0.58**	0.65**
Tongue	At rest	0.52**	0.51**
	Protrusion	0.36**	0.51**
	Elevation	0.49**	0.70**
	Lateral	0.46**	0.55**
	Alternate	0.79**	0.86**

	In speech	0.48**	0.71**
Intelligibility	Words	0.29**	0.43**
	In sentences	0.37**	0.50**
	In conversation	0.48**	0.59**
Total FDA-2 score		0.119**	0.10**

** Significant at p<0.01, * significant at p<0.05

5.6.2 Assessment results

5.6.2.1 Overall severity of oromotor impairment

Overall severity of oromotor impairment ranged from *normal* to *moderate*. Six participants (17.14%) presented with overall normal oromotor function (Figure 5.1).

The mean ($\bar{x}$) was calculated for each FDA-2 domain (Reflexes, Respiration, Lips, Palate, Laryngeal, Tongue, and Intelligibility). *Laryngeal* function was the most affected domain ($\bar{x}$ 3.49, ± 1.65), indicating overall mild impairment, followed by *Tongue* function ($\bar{x}$ 2.95, ± 1.24), *Respiration* ($\bar{x}$ 2.86, ± 1.45), *Reflexes* (including cough, swallow, and dribble/drool) ($\bar{x}$ 2.73, +/- 1.25), *Intelligibility* ($\bar{x}$ 2.43, ± 1.47), *Lips* ($\bar{x}$ 2.27, ± 0.67), and *Palate* ($\bar{x}$ 1.92, ± 0.63) (Table 5.5; Figure 5.2).

Figure 5-1 Severity of oromotor impairment in individuals with FRDA (n=35)

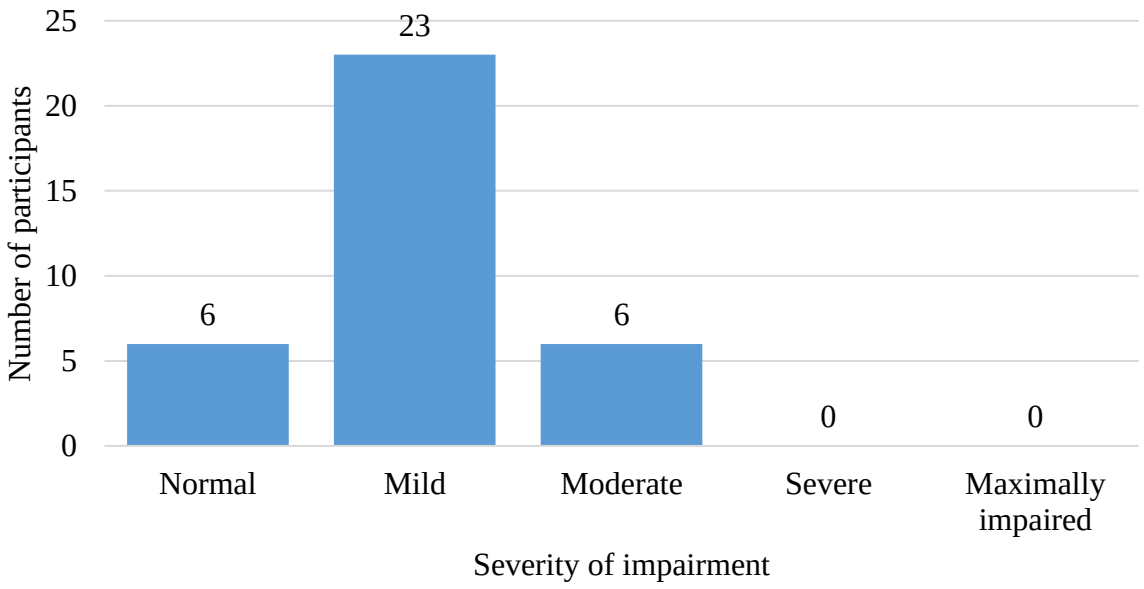
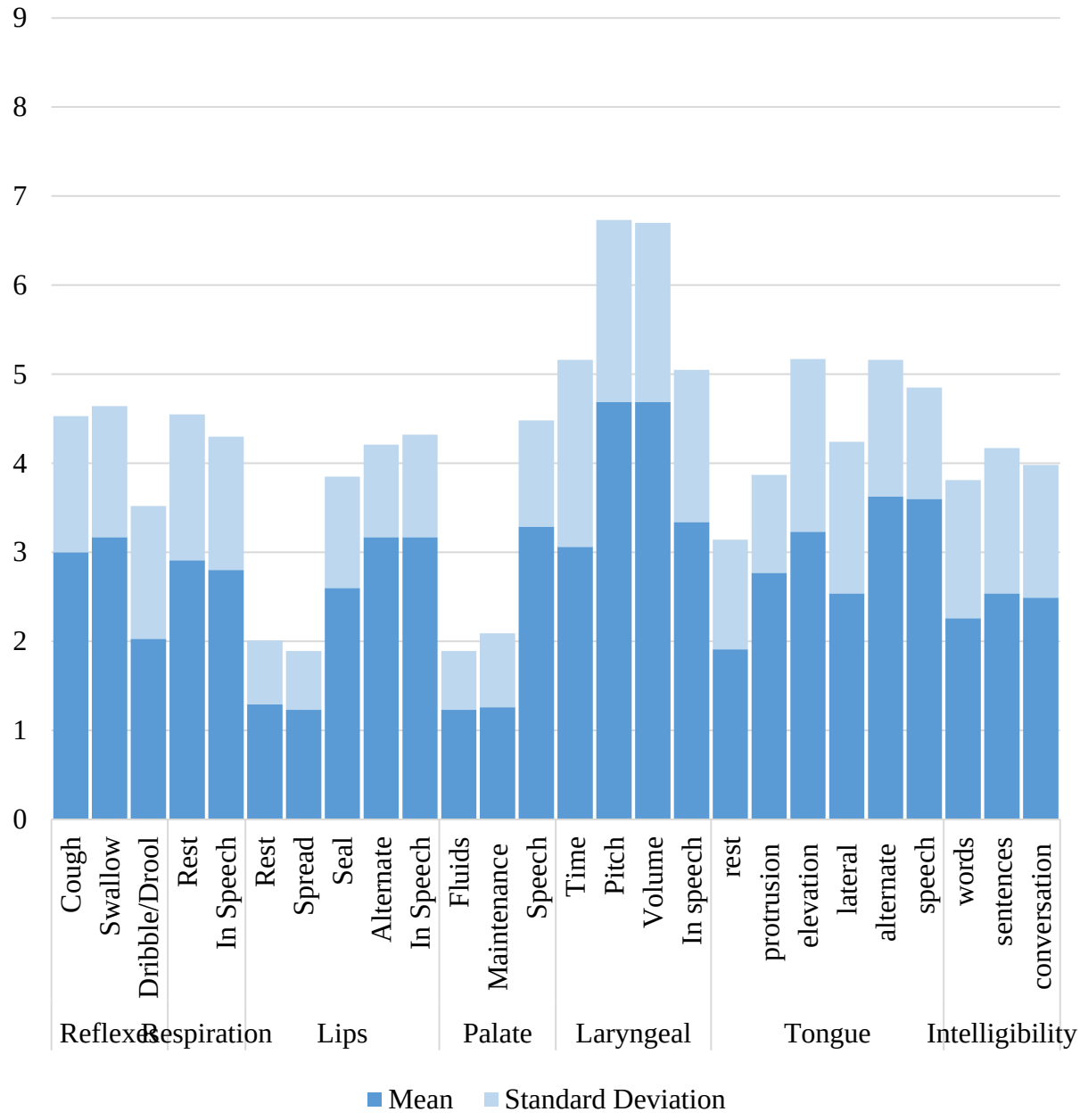


Table 5-3 Results of FDA-2 (n=35)

FDA-2 domains and sub-items		$\bar{x}$	σ	min	max	Overall domain $\bar{x} \pm \sigma$
Reflexes	Cough	3.0	1.53	1	7	2.73 ± 1.25
	Swallow	3.17	1.46	1	5	
	Dribble/Drool	2.03	1.48	1	5	
Respiration	Rest	2.91	1.63	1	7	2.86 ± 1.45
	In Speech	2.80	1.49	1	7	
Lips	Rest	1.29	0.71	1	3	2.29 ± 0.67
	Spread	1.23	0.65	1	3	
	Seal	2.60	1.24	1	5	
	Alternate	3.17	1.04	1	5	
	In Speech	3.17	1.15	1	5	
Palate	Fluids	1.23	0.65	1	3	1.92 ± 0.63
	Maintenance	1.26	0.82	1	5	
	Speech	3.29	1.18	1	5	
Laryngeal	Time	3.06	2.09	1	9	3.94 ± 1.65
	Pitch	4.69	2.04	1	7	
	Volume	4.69	2.01	1	7	
	In speech	3.34	1.70	1	7	
Tongue	Rest	1.91	1.22	1	5	2.95 ±1.24
	Protrusion	2.77	1.99	1	7	
	Elevation	3.23	1.93	1	7	
	Lateral	2.54	1.69	1	7	
	Alternate	3.63	.52	1	7	
	Speech	3.60	1.24	1	5	

Intelligibility	Words	2.26	1.54	1	5	2.43 ± 1.47
	Sentences	2.54	1.62	1	7	
	Conversation	2.49	1.48	1	7	
Total FDA2 score		71.89	26.27	34	126	

Figure 5-2 FDA-2 x̄ scores and σ (n=35)



5.6.2.2 Reflexes

Five participants of 35 (25.7%) presented with normal overall reflexive function, 22/35 (62.9%) with mild dysfunction, and 4/35 (11.4%) presented with moderate impairment.

Cough

Mild impairment of cough function (indicated by subjective reports of coughing when eating or drinking, or difficulty clearing the throat) was noted in 22/35 (62.9%) participants. Three participants (5.7%) presented with moderate impairment of cough (participant must take particular care when eating and drinking or chokes one or twice a day to frequently, or difficulty cleating phlegm), 2/35 (5.7%) presented with severe impairment of cough (chokes frequently on food or drink, is at risk of inhalation of oral intake, or chokes on own saliva) (Appendix Table 5.6).

Swallow

Participants were asked if they experienced swallowing difficulty and were observed eating a dry biscuit and drinking 125ml of water. Seven participants (20%) presented with functional swallow on bedside assessment and did not subjectively report dysphagia. Seventeen (48.6%) participants presented with mild swallowing impairment (participant reports some difficulty swallowing or eating and drinking is noted to be slow on bedside swallowing assessment), and 11/35 (31.42%) participants presented with moderate impairment (eating is markedly slow, some liquids or foods are avoided, or the participant can only swallow specially prepared food such as pureed or minced food). No participants presented with severe impairment (Appendix Table 5.7)

Dribble/Drool

The majority (22/35, 62.9%) of participants presented with adequate secretion management (Nine participants (25.7%) presented with mild impairment in secretion management (occasional dampness around the corners of the mouth or slight drooling when drinking), and 4/35 (11.4%) presented with moderate impairment (dribbles or drools when leaning forward or not concentrating) (Appendix Table 5.8).

5.6.2.3 Respiration

Seven participants of 35 (20%) presented with normal overall respiratory function, 22/35 (62.9%) with mild dysfunction, 5/35 (14.3%) with moderate dysfunction, and 1/35 (2.9%) presented with severe dysfunction.

At rest

At rest (observation of participant when sitting and not speaking, or when participant expiring as 'audibly and smoothly' as possible), 10/35 participants (28.6%) presented with normal function, 19/35 (54.3%) with mild dysfunction (inhalation not smooth or is shallow), 4/35 (11.4%) with moderate dysfunction (marked interruptions in inhalation or exhalation or difficulty in inhaling deeply), and 2/35 (5.7%) participants presented with severe impairment (little respiratory control) (Appendix Table 5.9).

Speech

Twenty-one participants (60%) presented with mild respiratory dysfunction in speech (very occasional breaks in fluency due to poor respiratory control, or participant may feel the need to stop and take a breath when speaking), 4/35 (11.4%) with moderate dysfunction (patient speaking quickly due to poor respiratory control), and 1/35 (2.9%) with severe respiratory dysfunction in speech (speaking on inhalation and exhalation) (Appendix Table 5.10).

5.6.2.4 Lips

Nine of the 35 participants (25.7%) presented with overall normal lip function, and 26/35 (74.3%) presented with mild dysfunction.

At rest and *spread*

At rest and with lips spread, 31/35 (88.6%) participants presented with no abnormality or asymmetry, and 4/35 (11.4%) presented with slight asymmetry however only noticeable to the skilled observer (Appendix Table 5.11).

Seal

Ratings of lip seal are based on the participant's capacity to maintain pressure with air blown into cheeks for 15 seconds, and produce 10 repetitions of /p/. Eleven participants (31.43%) participants presented with normal function, 19/35 (54.3%) with mild dysfunction (occasional air leakage, broken lip seal, or inconsistent plosion), and 5/35 (14.29%) with moderate dysfunction (air leakage or production of auditorily weak plosion) (Appendix Table 5.13)

Alternate

Participants are asked to repeat "oo ee" (/u i/) ten times and ratings are made based on performance. Three participants (8.57%) performed the task with no abnormality, 27/35 (77.1%) with mild dysfunction (faltering rhythm of variability in rounding and spreading

lips), 5/35 (14.29%) presented with laboured movement, indicative of moderate impairment (Table 5.14).

In Speech

In speech, 4/35 (11.43%) participants presented with normal lip function, 25/35 (71.43%) with mild impairment (weakness of briskness of lip movement), and 6/35 (17.14%) with moderate impairment (consistently poor movements acoustically represented as weak or explosive) (Appendix Table 5.15)

5.6.2.5 Palate

The majority (23/35, or 65.7%) of participants presented with overall normal palatal function, and 12/35 (34.4%) presented with mild dysfunction.

Fluids

Palatal function when drinking fluids, as measured by subjective reporting of food or drink coming out of the nose), was within normal limits for 31/35 (88.57%) of participants, and mildly impaired (patient has occasion difficulty) in 4/35 (11.43%) of participants (Appendix Table 5.16).

Maintenance

Palatal maintenance (symmetry and smoothness of movement) during phonation was within normal limits in 31/35 (88.6%) of participants, and mildly impaired (mild asymmetry) in 4/35 (11.4%) (Appendix Table 5.17).

In speech

Palatal function in speech is rated according to the amount of nasal resonance and nasal emission. This is facilitated by asking the patient to repeat /may pay/ and /nay bay/. Four participants (11.43%) presented with normal function, 23/35 (65.71%) with mild impairment, (slight hypernasality and/or imbalanced nasal resonance), and 8/35 (22.86%) presented with moderate hypernasality (Appendix Table 5.18).

5.6.2.6 Laryngeal

Four of the 35 participants (11.4%) participants presented with normal laryngeal function, 20/35 (57.1%) with mild laryngeal dysfunction, 10/35 (28.6%) with moderate dysfunction, and 1/35 (2.9%) with severe laryngeal dysfunction.

Time

Phonatory quality and endurance is measured by the participant's ability to produce a prolonged "ah" (/a/). Thirteen of the 35 participants (37.14%) presented with normal function (able to sustain "a*h*" for 15 seconds), 9/35 (25.71%) presented with mild impairment (sustained "*ah*" for 10 seconds), 11/35 (31.4%) with moderate impairment (five to 9 seconds), and 1/35 (2.9%) with severe impairment (unable to sustain /a/ for over three seconds) (Appendix Table 5.19).

Pitch

Pitch is evaluated by instructing the participant to sing at least six notes up a scale. Four participants (11.43%) presented with normal function, 10/35 (28.57%) with mild impairment (minor difficulty, pitch breaks or laboured), 8/35 (22.86%) participants presented with moderate impairment (four distinct pitch changes and uneven progression, 12/35 (34.28%) presented with severe impairment (minimal pitch change), and 1/35 (2.86%) participant with presented with maximal impairment (no change to pitch) (Appendix Table 5.20).

Volume

Ratings of volume are based on the participants' ability to count to five with increasing volume. Three participants (8.57%) presented with normal function, 10/35 (28.57%) with mild impairment (minimal difficulty), 11/35 (31.43%) with moderate impairment (noticeably uneven progression), and 11/35 (31.43%) with severe impairment (only limited change in volume) (Appendix Table 5.21).

In Speech

Six participants (17.14%) presented with normal function (effective and appropriate), 20/35 (57.14%) with mild impairment (voice is most effective), 7/35 (20%) with moderate impairment (voice requires effort and attention, deteriorates and can be unpredictable), and 2/35 (5.71%) with severe impairment (ineffective and inappropriate in most situations) (Appendix Table 5.22).

5.6.2.7 Tongue

Normal overall tongue function was observed in 8/35 (22.9%) of participants. Twenty-four of the 35 participants (68.6%) presented with mild impairment, and 3/35 (8.6%) presented with moderate impairment.

At rest

At rest, 18/35 (51.43%) of the participants presented with normal tongue function (no involuntary movement or asymmetry), 14/35(40.00%) with mild impairment (occasional involuntary movement of the tongue at rest), and 3/35 (8.57%) presented with a noticeable tongue deviation or apparent involuntary movement (Appendix Table 5.23).

Protrusion

To rate tongue protrusion the participant is instructed to protrude and retract the tongue 10 times. Sixteen participants (45.71%) presented with normal function (smooth movement), 8/35 (22.86%) with mild impairment (slow, between four to six seconds), 9/35 (25.71%) with moderate impairment (irregular movement, between six to 8 seconds), and 2/35 (57.14%) with severe impairment (more than eight seconds required to complete the task, or restricted tongue protrusion limited to the teeth) (Appendix Table 5.24).

Elevation

To measure tongue elevation the participant is directed to point their tongue toward their nose then move toward their chin, in sequence, five times. Ratings are made according to ease and completeness of the movement. Ten participants (28.57%) presented with normal function, 15/35 (42.86%) with mild impairment (moves well but slowly), 7/35 (20%) with moderate impairment (laboured or incomplete movement), and 3/35 (8.57%) with severe impairment (tongue movement limited to one direction only) (Appendix Table 5.25).

Lateral

Lateral movement of the tongue is rated by instructing the patient to move their tongue from one side of the mouth to the other (outside of the lips) five times. Eighteen participants (51.43%) of participants, 10/35 (28.57%) with mild impairment (slow movement, between 5 to 6 seconds), 6/35 (17.14%) with moderate impairment (laboured or incomplete movement), and 1/35 (2.86%) with severe impairment (moves to one side only or is unable to maintain) (Appendix Table 5.26).

Alternate

Alternate movement (ten repetitions of “ka la” as quickly as possible) is considered in terms of coordination and speed of movement. Four of the participants (11.43%) presented with normal function, 17/35 (48.57%) with mild impairment (slight incoordination or reduction in speech), 12/35 (34.39%) with moderate impairment (one sound is well articulated by the other is poorly presented or task deteriorates), and 2/35 (5.71%) with severe impairment

(changes in tongue movement but little differentiation between the sounds) (Appendix Table 5.27).

In speech

Tongue function is speech is addressed in conversation and facilitated by directing the participant to repeat the sentence "*Kenneth's dog took ten tiny ducks today*". Three participants (8.57%) presented with normal function, 18/35 (51.43%) with mild impairment (slightly inaccurate), and 14/35 (40%) with moderate impairment (slow alternating movements making speech laboured) (Appendix Table 5.28).

5.6.2.8 Intelligibility

Overall intelligibility in conversational speech was functional (impairment noted only by a trained listener) in 16/35 (45.7%) participants. Fifteen (42.9%) presented with mildly impairment intelligibility, and four (11.4%) presented with moderately impaired speech intelligibility.

Words

Intelligibility at word level is assessed by evaluating the speech of patients reading aloud 10 randomly selected single words. Eighteen participants (51.43%) presented with normal function (production of 10 intelligible words, as interpreted by a trained therapist), 11/35 (31.43%) with mild impairment (words interpreted with particular care taken in listening), and 6/35 (17.14%) with moderate impairment (production of six to nine intelligible words) (Appendix Table 5.29).

Sentence

Fifteen participants (42.86%) presented with normal function (10 intelligible phrases correctly interpreted by the therapist), 12/35 (34.29%) with mild impairment (particular care taken), 6/35 (17.14%) with moderate impairment, and 1/35 (2.86%) with severe impairment (Appendix Table 5.30).

In conversation

In conversational speech, 13/3 participants (37.14%) presented with intelligible speech, 18/35 (51.43%) with mild impairment (abnormal but intelligible speech), 3/35 (*8.57%) with moderate impairment (understood half of the time), and 1/35 (2.86%) with severe impairment (only occasional words decipherable) (Appendix Table 5.31).

5.7 Relationship between FRDA clinical parameters and oromotor dysfunction

5.7.1 Overall oromotor function

Overall oromotor dysfunction (total FDA-2 score) was positively correlated with GAA1 length (ρ=0.37, $p<0.05$), FARS score (ρ =0.64, $p<0.01$), and disease duration (ρ =0.74, $p<0.01$). A negative correlation was observed between total FDA-2 score and age at disease onset (ρ=-0.37, p>0.0%) (Appendix Table 5.4).

5.7.2 FDA-2 domains and subtests

FARS and disease duration correlated with all FDA-2 domains, Overall tongue dysfunction correlated with GAA1 length (ρ=0.45, $p<0.01$), FARS (ρ=0.48, $p<0.01$), age at onset (ρ=-0.52, $p<0.01$), and disease duration (ρ=0.58, $p<0.01$) (Table 5.4).

5.7.2.1 Reflexes

Disease duration positively correlated with all subtests (*Cough*: ρ=0.50, $p<0.01$; *Swallow* ρ=0.61, $p<0.01$; and *Dribble/Drool*: ρ=0.39, $p<0.05$). FARS was positively correlated to swallowing function (*Swallow*: ρ=0.46, $p<0.05$), and age at assessment positively related to *Cough* (ρ=0.38, $p<0.05$).

5.7.2.2 Respiration

Respiratory function in *Speech* positively related to FARS (ρ=0.68, $p<0.01$), age at disease onset (ρ=-0.41, $p<0.05$), and disease duration (ρ=0.62, $p<0.01$). No significant correlations were obtained between respiration *at rest* and FRDA clinical parameters.

5.7.2.3 Lips

Lip seal was the only item significantly related to GAA1 length (ρ=0.34, $p<0.05$). FARS score positively correlated with *Lip seal* (ρ=0.42, $p<0.05$), *Alternate* function (ρ=0.55, $p<0.01$), and lip function in *Speech* (ρ=0.53, $p<0.01$). The same FDA-2 items positively correlated with disease duration (seal: ρ=0.60, $p<0.01$; alternate: ρ=0.50, $p<0.01$; and in speech: ρ=0.54, $p<0.01$).

5.7.2.4 Palate

FARS positively correlated with palate *maintenance* (ρ=0.46, $p<0.05$) and palatal function *in speech* (ρ=0.65, $p<0.01$). Age at assessment was significantly correlated with palatal function *in speech* (ρ=0.49, $p<0.01$). Disease duration was positively related to *maintenance* (ρ=0.41, $p<0.05$) and palatal function *in speech* (ρ=0.64, $p<0.01$).

5.7.2.5 Laryngeal

Laryngeal parameters most related to disease duration (*time*: ρ=0.56, p<0.01); *pitch*: p=0.65, p<0.01; *volume*: ρ=0.62, p<0.01; *In speech*: ρ=0.56, p<0.01) and FARS (*time*: ρ=0.46, p<0.05); *pitch*: p=0.52, p<0.01; *volume*: ρ=0.61, p<0.01; *In speech*: ρ=0.46, p<0.01). Age at disease onset negatively correlated with *time* (ρ=-0.37, p<0.05). Age at assessment positively correlated with *pitch* (ρ=0.37, p<0.05) and *volume* (ρ=0.48, p<0.01).

5.7.2.6 Tongue

Tongue function parameters were related to GAA1, FARS, age at onset, and disease duration. GAA1 positively correlated with *protrusion* (ρ=0.35, p<0.05), *elevation* (ρ=0.49, p<0.01), *lateral* (ρ=0.49, p<0.01), and *alternate* movement (ρ=0.55, p<0.01). FARS positively related to *alternate* (ρ=0.57, p<0.01) and tongue function *in speech* (ρ=0.48, p<0.05). Age at onset negatively correlated with *protrusion* (ρ=-0.46, p<0.01), *elevation* (ρ=-0.59, p<0.01), *lateral* (ρ=-0.37, p<0.05), *alternate* (ρ=-0.58, p<0.01) and *in speech* (ρ=-0.36, p<0.05). Disease duration positively related to *protrusion* (ρ=0.40, p<0.05), *elevation* (ρ=0.50, p<0.01), *lateral* (ρ=0.50, p<0.01), *alternate* (ρ=0.63, p<0.01) and *in speech* (ρ=0.60, p<0.01).

5.7.2.7 Intelligibility

Intelligibility at *word, sentence* and *conversation* level related to FARS (words: ρ=0.45, p<0.05); sentences: p=0.53, p<0.01; in conversation: ρ=0.59, p<0.01) and disease duration (*words*: ρ=0.60, p<0.01); *sentences*: p=0.64, p<0.01; *in conversation*: ρ=0.61, p<0.01). Age at assessment positively correlated with intelligibility at *sentence* level (ρ=0.38, p<0.05).

Table 5-4 Relationships between FDA-2 domains and FRDA

	Reflexes	Respiration	Lips	Palate	Laryngeal	Tongue	Intelligibility	Total
GAA1	0.13	0.26	0.25	0.09	0.32	0.45**	0.22	0.37*
GAA2	-0.07	0.15	0.09	0.12	0.14	0.19	0.00	0.11
FARS	0.48**	0.54**	0.52**	0.66**	0.63**	0.48**	0.55**	0.64**
Age at disease onset	-0.18	-0.27	-0.34*	-0.17	-0.32	-0.52**	-0.25	-0.37*
Age at assessment	0.37*	0.38*	0.18	0.45**	0.36*	0.03	0.39*	0.34
Disease duration	0.60**	0.53**	0.57**	0.67**	0.71**	0.58**	0.66**	0.74**

**Significant at p<0.0.1 * Significant at p<0.05

Table 5-5 Relationships between FDA-2 items and FRDA

		GAA1	GAA2	FARS	Age at onset	Age at assessment	Disease duration
Reflexes	Cough	0.17	-0.14	0.33	-0.06	0.38*	0.50**
	Swallow	0.10	0.01	0.46*	-0.22	0.30	0.61**
	Dribble/Drool	0.04	-0.09	0.35	-0.19	0.23	0.39*
Respiration	Rest	0.19	0.09	0.32	-0.14	0.28	0.36
	In Speech	0.28	0.16	0.68**	-0.41*	0.39*	0.62**
Lips	Rest	-0.04	0.04	-0.01	-0.10	-0.21	-0.08
	Spread	-0.12	0.15	0.19	0.09	0.11	0.08
	Seal	0.34*	0.01	0.42*	-0.26	0.24	0.60**
	Alternate	0.18	0.04	0.55**	-0.46**	0.24	0.50**
	In Speech	0.32	0.19	0.53**	-0.43**	0.13	0.54**
Palate	Fluids	0.17	-0.24	-0.25	-0.02	0.19	0.24
	Maintenance	-0.04	0.07	0.46*	-0.27	0.07	0.41*
	Speech	0.00	0.17	0.65**	-0.08	0.49**	0.64**

Laryngeal	Time	0.24	0.03	0.46*	-0.37*	0.11	0.56**
	Pitch	0.33	0.08	0.52**	-0.31	0.37*	0.65**
	Volume	0.27	0.31	0.61**	-0.17	0.48**	0.62**
	In speech	0.21	0.08	0.46*	-0.25	0.26	0.56**
Tongue	At rest	-0.07	-0.06	0.22	-0.16	0.00	0.08
	Protrusion	0.35*	0.15	0.35	-0.46**	-0.09	0.40*
	Elevation	0.49**	0.15	0.36	-0.59**	-0.14	0.50**
	Lateral	0.49**	0.20	0.36	-0.37*	0.02	0.50*
	Alternate	0.55**	0.28	0.57**	-0.58**	0.13	0.63**
	In speech	0.31	0.06	0.48*	-0.36*	0.22	0.60**
Intelligibility	Words	0.20	0.01	0.45*	-0.24	0.35	0.60**
	In sentences	0.18	0.01	0.53**	-0.26	0.38*	0.64**
	In conversation	0.25	-0.01	0.59**	-0.28	0.35	0.61**

**Significant at p<0.0.1, * Significant at p<0.05

Figure 5-3 Relationship between FDA-2 total score and GAA1 length

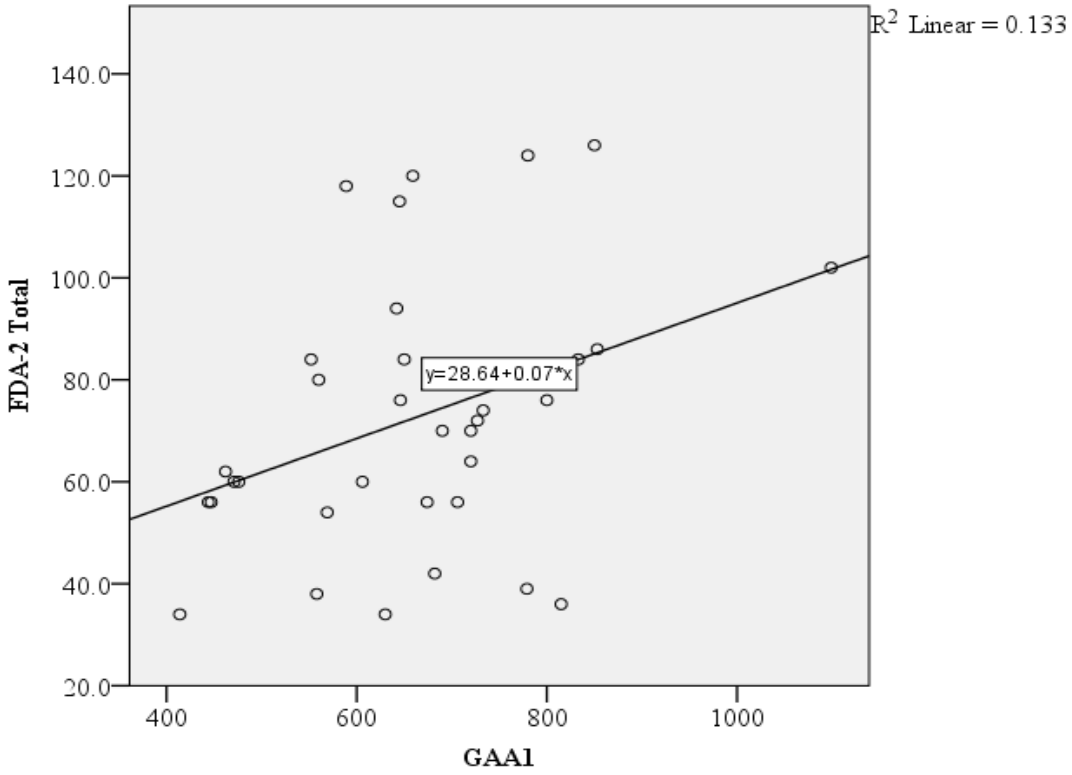


Figure 5-4 Relationship between FDA-2 total score and FARS

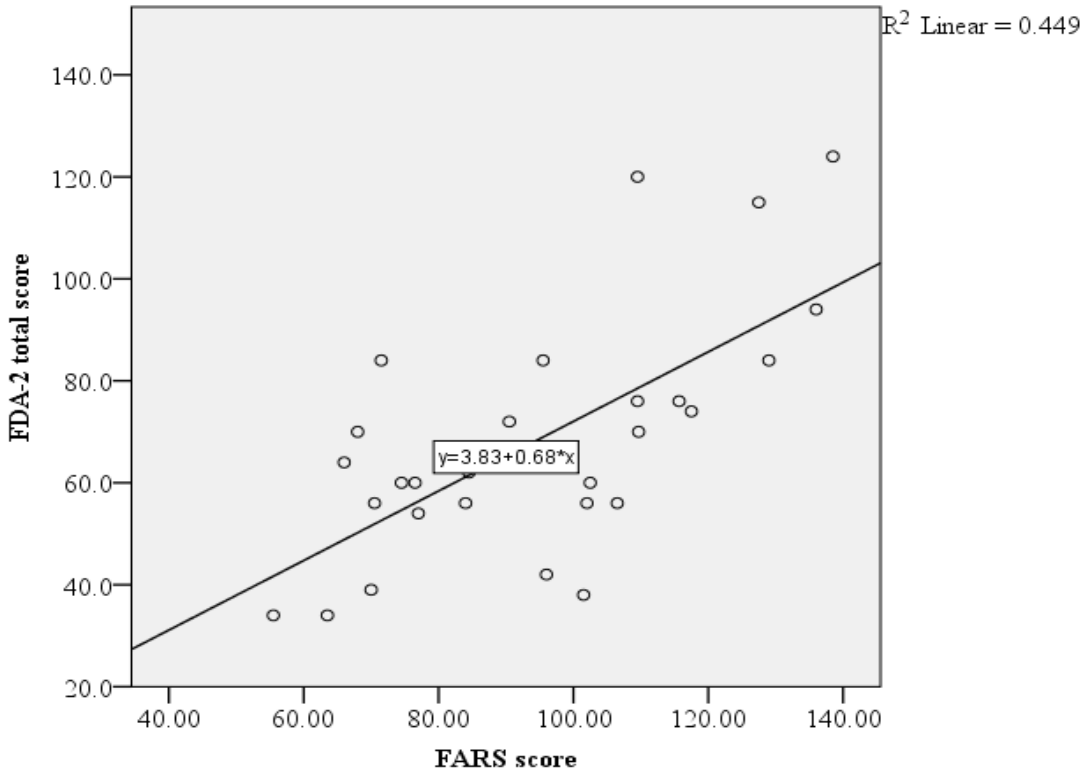


Figure 5-5 Relationship between FDA-2 total score and age at disease onset

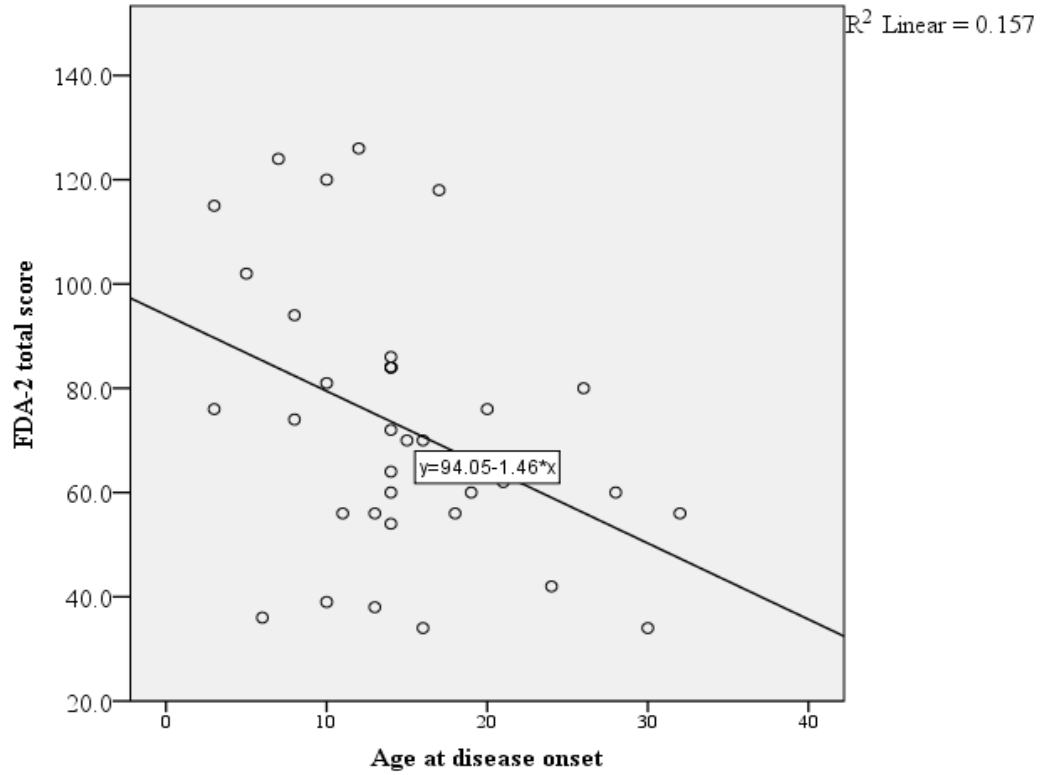
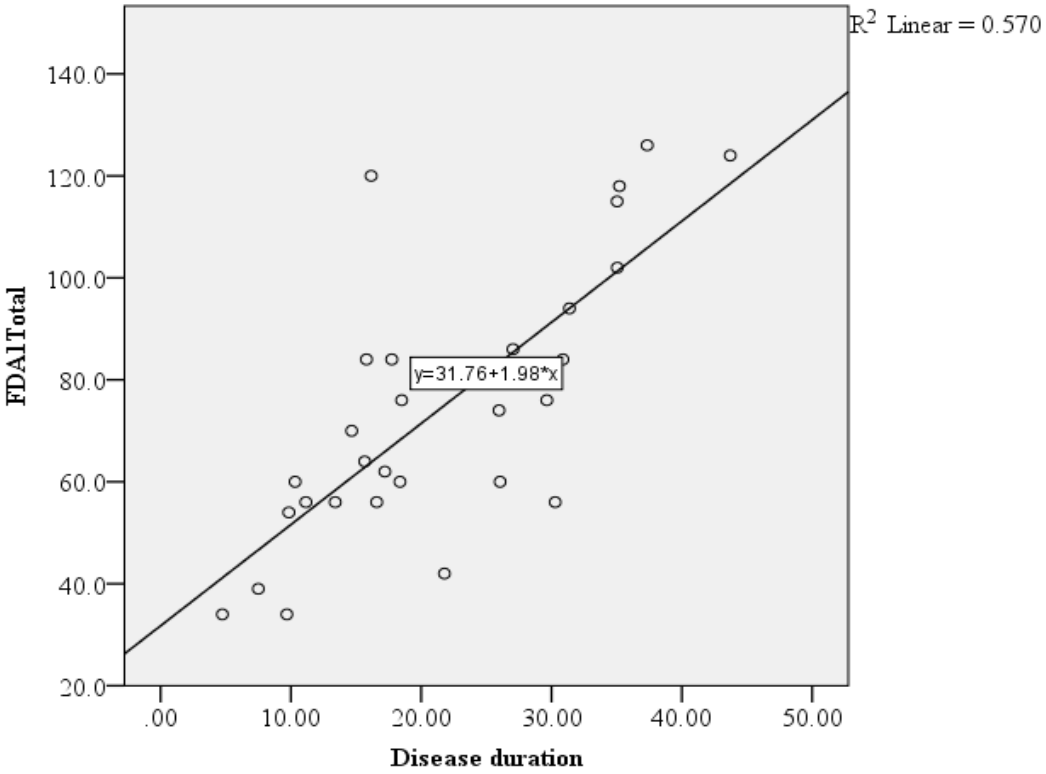


Figure 5-6 Relationship between FDA-2 total score and disease duration



5.8 Discussion

This study aimed to strengthen understanding of oromotor function in FRDA via systematic characterisation using the clinical standard of assessment, as well as determine the relationships between oromotor impairment and FRDA clinical markers. Impairment was observed across all oromotor domains, with Laryngeal function the most severely affected, followed by Tongue function and Respiration, thus confirming the primary hypothesis. Oromotor dysfunction related to disease severity and duration which supports the second hypothesis of this study. Correlations were also observed between FDA-2 sub-items and GAA1 length, age at disease onset, and disease severity, therefore confirming the second hypothesis. GAA2 length did not relate to oromotor dysfunction.

5.8.1 Characteristics of FRDA-related oromotor impairment

This study complements and extends on previous research pertaining to oromotor function in individuals with FRDA. Previous research reported a plethora of oromotor impairments in the FRDA population, including lingual, laryngeal, reflexive, and palatal dysfunction, however in only small samples of participants (Eigentler et al., 2012; Poole et al., 2015). The predominant feature of oromotor dysfunction investigated in the literature in FRDA is speech, which is characterised by imprecise consonant production, reduced pitch variation, variability in laryngeal function, reduced loudness, hypernasality, and reduced phrase length and limited breath support (Folker et al., 2010; Folker et al., 2012). In this study mild to moderate laryngeal dysfunction was evident in 88.6% of participants in the present study. Close to 89% of participants presented with poorly executed labial sounds in speech, whilst 91.43% presented with reduced precision of lingual sounds in speech. Overall, 62.86% participants presented with a degree of speech unintelligibility in conversation. In relation to swallowing, participants in this study reported coughing and choking with oral intake, and other subjective reports of dysphagia symptoms. Participants also reported modifying their diet to accommodate for swallowing impairment when probed on FDA-2 assessment, in line with previous research by Vogel and colleagues (2014).

There was no control group included in the study, and thus data was considered using the normative sample included during standardisation of the FDA-2 included 194 healthy individuals (age range 15 to 97 years) divided into a younger and older group (< 60 > years of age), with 90% of participants in each group reported to have scores an optimal rating on the FDA-2 (Enderby, 2011). Only 6/25 participants (17.14%) participants with FRDA scored

an overall score of normal, demonstrating the discrepancy between FRDA and healthy populations in regarding to oromotor dysfunction.

5.8.2 Relationships between FRDA clinical parameters and oromotor impairment

The severity of oromotor impairment in FRDA increases in line with disease duration and severity. This research reveals significant correlational relationships between overall oromotor dysfunction (total FDA-2 score) and FRDA severity and duration, age at disease onset, and GAA1 length. Disease severity and duration related to all domains of the FDA-2. Similar correlations were noted in the study by Eigentler and colleagues (2012). The length of GAA2 did not relate to oromotor impairment in this study, however GAA2 has been previously related to palatal dysfunction (Poole et al., 2015) and perceptual ratings of overall dysarthria severity (Folker et al., 2009).

5.8.3 Aetiology and clinical course of oromotor impairment in FRDA

FRDA is characterised by large variation in the rate of disease progression, age of onset and presence of non-universal disease symptoms that reflect widespread degeneration. In FRDA there is degeneration of the dorsal root ganglia, posterior columns of the spinal cord, spinocerebeller tracts, corticospinal and corticobulbar motor tracts, and degeneration of the large sensory fibres in the peripheral nerves (Harding et al., 2016; Koeppen, 2011). Given widespread pathology, substantial variation in the oromotor impairment of individuals with FRDA is expected. Speech is a complex behaviour encompassing a multitude of neural events to facilitate the complex coordination of the articulatory muscles and integration of the motor system. The planning and programming for the sequencing of speech muscle movement relies heavily on the pre-frontal and pre-motor areas, whilst the motor execution is reliant on several cranial nerve nuclei and a number of cerebral structures including the Broca's area, sensorimotor cortex, and the basal ganglia (Damico, Müller, & Ball, 2012). The cerebellum influences the production of motor speech via afferent and efferent feedback circuits, and thus lesions of the cerebellum may disturb volitional movements, including speech. It was unsurprising to see widespread oromotor impairment in the present study. The laryngeal and reflexive impairment is demonstrative of the corticobulbar degeneration associated with FRDA (Koeppen & Mazurkiewicz, 2013), further affected by cerebellar degeneration and impaired motor control in diadochokinetic (DDK) tasks (for example, rapid repetitions of /p/ and /u i/ (in the alternating task of the Lip domain on the FDA-2).

The cerebellum also plays a role in executive functioning (Ackermann, Mathiak, & Riecker, 2007). Cerebellar degeneration with associated function changes in the fronto-cerebellar networks is a hallmark feature of FRDA (Delatycki et al., 2000; Harding et al., 2016) and manifests in functional changes in the fronto-cerebellar networks affecting executive functioning (Harding et al., 2016). Motor planning is known to be affected in FRDA in limb movement (Akhlaghi et al., 2012; Corben et al., 2010; Corben et al., 2011; Harding et al., 2016; Zalesky et al., 2014), and thus it is judicious to assume similar manifestations would occur in speech production. It is also possible the reduced performance in DDK tasks and in conversational speech in this study arise due to learned compensatory behaviours. In their study, Folker and colleagues (2011b) revealed prolonged articulatory durations impacting on speech in FRDA rather than slowed motor execution, possibly due to cerebellar and corticobulbar disturbances, or a results of individuals with FRDA consciously slow their speech rate (resulting in larger articulatory movements) to facilitate speech clarity and increase intelligibility. This may transcend into other speech tasks assessed on the FDA-2 in which participants must perform a number of directed facial movements, and thus affect performance.

5.8.4 Limitations of the present study

The present study is perceptual only and does not involve an instrumental measure of oromotor function, such as EMA or other devises. However, the non-instrumental nature of the assessment used in this study makes it effective for clinicians to replicate in everyday practice. Further, no control group was included in this study due to time constraints. Further work should focus on comparing the oromotor function of individuals with FRDA with comparative health control data.

5.8.5 *Clinical implications of this study*

It is recommended individuals with FRDA undergo regular assessment of oromotor function from the time of diagnosis and thereafter (Corben et al., 2014). The current study reiterates the importance of targeted intervention of FRDA-related speech impairment given the widespread and variable oromotor dysfunction. Behavioural management remains the most suitable intervention option for FRDA-related dysarthria with focus on high intensity and frequency in line with principles of motor learning (Corben et al., 2014; Ludlow et al., 2008). Individuals who present with concomitant voice impairment (laryngeal dysfunction) should also be provided education on vocal hygiene and safe voice use (Corben et al., 2014).

Environmental considerations should also be made, including reducing background noise or augmenting communication using a voice output device. Communication partner training should also be provided in order to maximise and support any speech intervention.

5.9 Summary

Oromotor dysfunction is a known sequela of FRDA and is progressive given strong relationships between FDA-2 parameters and measures of disease severity and duration. It is judicious to assume these oromotor manifestations will translate to impairment of swallowing, which is for further investigation. This study is an important precursor to a systematic evaluation of swallowing function in FRDA and results will be used to determine potential predictors of airway compromise during swallowing in the population.

Chapter 6 Study 3 - A videofluoroscopic analysis of swallowing in individuals with FRDA

6.1 Research questions

Dysphagia is prevalent in the FRDA population and is known to impose significant burden and negatively impact on QOL (Vogel et al., 2014; Chapter 4). There are no studies investigating FRDA-related dysphagia using instrumental analysis (considered best clinical practice) nor have predictors of penetration/aspiration been explored in this population. This is critical given 10% of deaths occur secondary to pneumonia in the FRDA population (Tsou et al., 2011). The following questions remain unanswered:

1. What are the oral and pharyngeal phase characteristics of dysphagia in individuals with FRDA?
2. What is the prevalence of significant airway compromise in individuals with FRDA?
3. Are there relationships between dysphagia and indicators of disease severity (including age at time of disease onset and assessment, disease duration, GAA repeat size on the smaller (GAA1) and larger (GAA2) *FXN* allele, and disease severity [FARS score])?
4. What are the predictors, if any, of airway entry compromise during swallowing in individuals with FRDA?

6.2 Rationale

There are no detailed clinical studies of FRDA-related swallowing impairment. This research aims to improve understanding of the condition by determining the severity and nature of dysphagia in FRDA. Findings will elucidate the natural history of dysphagia in FRDA, and inform management and therapeutic intervention strategies for the disease.

6.3 Aims and hypotheses

Aim 1 - characterise the swallow physiology of individuals with FRDA

Hypothesis 1 - Individuals with FRDA present with oral and pharyngeal phase swallowing deficits.

Aim 2 - Determine the prevalence of significant airway penetration and/ or aspiration in individuals with FRDA.

Hypothesis 2 - Penetration and/or aspiration will be observed on VFSS in individuals with FRDA.

Aim 3 - Determine the relationship between dysphagia and disease parameters

Hypothesis - Disease severity, duration and age of onset will significantly correlate with dysphagia severity determined by an instrumental assessment

Aim 4 -Determine predictors of significant airway compromise in individuals with FRDA.

Hypothesis – It is hypothesised predictors of significant airway compromise will include disease duration and severity, laryngeal function (a measured on the FDA-2), and total Swal-QOL score.

6.4 Background

The underlying mechanisms and characteristics of dysphagia in FRDA are not well described. Vogel and colleagues (2014) published the only study to date investigating swallowing function in individuals with FRDA using non-instrumental assessment techniques. Signs of dysphagia were reported in 35/36 (97.22%) of the cohort, with common symptoms including coughing/choking on thin fluids (21/36, or 58.33%) and dry, crumbly or solid foods (14/36, 38.89%). Schöls and colleagues (1997) reported an inverse relationship between GAA1 and the onset of dysphagia ($r=-0.42$, $p<0.09$, $n=102$ consecutively recruited individuals with FRDA), meaning those with a larger GAA repeat size on the smaller allele had earlier onset of dysphagia. No studies have investigated FRDA-related dysphagia using instrumental swallowing analysis (the clinical gold standard), nor have predictors of significant airway penetration and/or aspiration been explored in this population. This is critical given 10% of deaths in FRDA are attributed to pneumonia (Tsou et al., 2011), a common sequela of dysphagia.

6.5 Methods

6.5.1 Participants

Sixty individuals homozygous for an *FXN* intron 1 GAA expansion were recruited consecutively through the Friedreich Ataxia Clinic in Melbourne, Australia. All participants were screened for dysphagia via a clinical case history and swallowing quality of life questionnaire, the Swal-QOL (McHorney et al., 2000). The results of Swal-QOL analysis are presented in (Chapter 4). From this initial cohort, 59 were identified as having suspected dysphagia and were referred for oromotor assessment (Frenchay Dysarthria Assessment (2nd edition) (FDA-2), Enderby, 2011) and VFSS. Thirty-five participants (58.33%) went on to have FDA-2 assessment, and 38 (63.33%) underwent VFSS. Of the remaining 22 individuals,

12 did not participate in further assessment due to logistical reasons (such as transport issues), eight declined further assessment, and one participant did not present with signs of dysphagia on Swal-QOL or case history, therefore did not meet criteria for administration of VFSS or FDA-2. Thirty participants (50%) completed all assessments (Swal-QOL, FDA-2 and VFSS). Sixteen (26.67%) participants completed the Swal-QOL only, 5/60 (8.33%) completed the Swal-QOL and FDA-2 assessment, and 7/60 (11.67%) completed a combination of the Swal-QOL and VFSS. One (1.67%) participant participated in VFSS only after not returning the Swal-QOL, however had previously reported dysphagia on case history. Table 6.1 outlines the clinical characteristics of the 38 individuals who underwent VFSS.

On average, VFSS was conducted 22.8 days (±16.6) after administration of the Swal-QOL, and 32.7 days (±22.8) after administration of the FDA-2. Efforts were made to conduct all assessments on the same day, however this was not always possible. The Swal-QOL was generally completed prior to the participants attending the FRDA clinic at Monash Medical Centre, or on the day of the clinic appointment. In most cases, VFSS was conducted on the day of the participant's visit to the FRDA clinic. If the participant lived locally and had access to transport, VFSS was scheduled at the next possible appointment time, as close as possible to the date of the participant's clinic visit. Due to the competing time demands of a busy clinical day, the FDA-2 was completed after the VFSS in the patient's home. For patients admitted to hospital for rehabilitation, all three assessments were completed in on the same day.

6.5.2 Assessment

6.5.2.1 VFSS

Swallowing function related to FRDA was evaluated using VFSS, the preferred method of instrumental analysis as it allows complete and dynamic evaluation of all phases of the swallow in real-time (Rugiu, 2007). Additionally, VFSS is the only form of instrumental swallowing assessment that allows for direct observation of timing, amount and severity of aspiration (Mann & Hankey, 2001) (further detailed in Chapter 3).

VFSS Procedure

VFSS was conducted at Monash Medical Centre or the Kingston Centre (both in Melbourne, Australia). Images were taken in the lateral view with the participant sitting upright. The fluoroscopic field included the anterior surface of the lips, the hard palate superiorly, the

postural border of the spinal column, and the space below the larynx. Measures were put in place to replicate everyday feeding practices as closely as possible. Individuals were encouraged to self-feed during the VFSS and were seated in their own wheelchair when possible. Those who were mobile were seated in a standard chair. Three consistencies were trialled, including unmodified/regular fluids (5ml bolus and consecutive sips), puree (up to five teaspoons of Foster Clark Custard®), and biscuit (Arnott's Savoy® Biscuits with a thin spreading of jam mixed with barium powder). The barium powder was MCI Forrest X-OPAQUE-HD barium sulphate suspension formulation. Of the 38 participants who underwent VFSS, two did not trial puree consistency due to intolerance to custard. A consistent recipe was used for each VFSS procedure and substances were presented in a random order to control for fatigue, and other possible effects related to bolus presentation. The worst performance in terms of significant airway penetration and/or aspiration for each swallow was recorded on the Penetration-Aspiration Scale (PAS) (Rosenbek, Robbins, et al., 1996).

Each VFSS was conducted jointly by a qualified Speech Pathologist trained in VFSS administration and interpretation (the author), and a Radiographer. Each VFSS was rated by the author, with repeat ratings conducted ($\bar{x}$ 102.2 days, σ 14.24 days apart) to establish intrarater reliability. A second rater (also an experienced clinician) provided ratings to establish interrater reliability. The second rater was blinded to the participant and was trained by the author, in line with the recommendation made by Scott and colleagues (1998), where raters are able to discuss their decisions, thus establishing a degree of consensus before rating.

6.5.2.2 VFSS interpretation

VFSS was interpreted using the Bethlehem Assessment Scale (BAS) (Scott, Perry, & Bench, 1998) and the Penetration-Aspiration Sale (PAS) (Rosenbek, Robbins, et al., 1996). Dysphagia severity was determined using the Dysphagia Outcome Severity Scale (DOSS) (O'Neil, Purdy, Falk, & Gallo, 1999)

The Bethlehem Assessment Scale (BAS) (Scott, 1999)

The BAS is a measure of physiological swallowing function. Each item on the BAS is guided by a four point rating scale which increases in line with impairment severity and contains clear descriptors for each component (Scott et al., 1998). Areas of assessment include *Lip Function, Tongue Function, Jaw Function, Soft Palate Function, Reflex Initiation,*

Aspiration, Residue in the Valleculae, Residue in the Pyriform Sinuses, Pharyngeal Function, and *Cricopharyngeal Function*.

The Penetration-Aspiration Scale (PAS) (Rosenbek, Robbins, et al., 1996)

The PAS is an 8-point interval scale describing penetration and aspiration events. Scores are determined by the extent of material entry into the airway and whether or not the material is expelled. The PAS has high interrater reliability (ICC 0.96, with 95% CI) (Rosenbek, Robbins, et al., 1996). Possible PAS scores include:

PAS Score	Description	Level of airway protection
1	Material does not enter airway	Complete airway protection
2	Material enters the airway, remains above the vocal folds, and is ejected from the airway	Penetration
3	Material enters the airway, remains above the vocal folds, and is not ejected from the airway.	
4	Material enters the airway, contacts the vocal folds, and is ejected from the airway	
5	Material enters the airway, contacts the vocal folds, and is not ejected from the airway	
6	Material enters the airway, passes below the vocal folds, and is ejected into the larynx or out of the airway	Aspiration
7	Material enters the airway, passes below the vocal folds, and is not ejected from the trachea despite effort	
8	Material enters the airway, passes below the vocal folds, and no effort is made to eject	

The Dysphagia Outcome Severity Scale (DOSS) (O'Neil et al., 1999)

The DOSS is a seven point scale of functional dysphagia severity and considers the level of independence, nutrition type, and diet texture and consistency required. The DOSS has strong interrater reliability of 90% and intrarater reliability of 93% (O'Neil et al., 1999). The levels of function included in the DOSS include:

Level	Description
1	Severe dysphagia - no oral intake;
2	Moderately severe dysphagia - maximum assistance or use of strategies with partial oral intake only (tolerated at least one consistency safely with total use of strategy)
3	Moderate dysphagia - total assist, supervision or strategies, two or more consistencies restricted
4	Mild-moderate dysphagia - intermittent supervision/cueing, one or more consistencies restricted
5	Mild dysphagia - Distant supervision, may need one diet consistency restricted
6	Within functional limits/modified independence
7	Normal in all situations

6.5.3 Incidence of chest infection in individuals with FRDA

To explore the clinical significance of aspiration in the FRDA population, a retrospective audit was conducted of clinical reports to determine the incidence of chest infection in individuals with FRDA. Clinical data from 587 Speech Pathology reports (159 patients attending the Friedreich Ataxia Clinic (Monash Health, Melbourne, Australia) between the years 2005 to 2015) were reviewed. Data pertaining to the incidence of patient-reported chest infection were collected and analysed. These data were considered to better understanding of the clinical relevance of dysphagia in FRDA.

6.5.4 Statistical analysis

Swallowing impairment

Descriptive statistics were used to define the observed swallowing deficits, and report frequency of significant airway penetration and/or aspiration as evident on VFSS (interpreted using the PAS and the aspiration domain of the BAS). DOSS scores are also reported.

Relationships between swallowing impairment and FRDA clinical parameters

Spearman's rho (ρ) correlations were used to investigate the relationship between swallowing function and other FRDA clinical parameters including GAA repeat length on both alleles, disease severity (as measured by the FARS) (Subramony et al., 2005), age at onset and disease duration (in years). This was the most appropriate correlation to use given the non-parametric nature of the data.

Predictors of significant airway penetration and/or aspiration in individuals with FRDA

To investigate predictors of airway compromise during swallowing, data from participants undergoing VFSS were split into two groups: individuals with and without evidence of significant airway penetration and/or aspiration, as determined by the PAS. A PAS score ≥ 3 was deemed to be clinically significant. This cut off was determined based on results of a study by Robbins and colleagues (1999) where 99% of healthy individuals (n=95) scored <3 on VFSS (Robbins, Coyle, Rosenbek, Roecker, & Wood, 1999). The clinical and behavioural differences between these independent groups were explored using independent sample *t* tests.

Predictors of airway compromise during swallowing were explored using two methods of regression analysis (logistic and multiple regression) and the PAS data was considered both as categorical and continuous data.

For the logistic regression, participants were dichotomised into two groups (those who demonstrated significant airway penetration/aspiration [PAS>3], and those who did not) with significant airway penetration/aspiration (PAS>3) treated as the dependent variable.

PAS scores were also considered as a continuous variable using multiple progression for each consistency trialled on VFSS (fluid, puree and biscuit) to investigate differences in the predictability of significant airway penetration/aspiration across different types of food and fluid.

Reliability

Intrarater and interrater reliability were determined using Gwet's Agreement Coefficient (GAC) (Gwet, 2015) - an index of agreement between measurements which corrects for the

amount of agreement expected to have occurred due to chance. Values were interpreted according to values stipulated by Viera and Garrett (2005), where < 0 = *Less than chance agreement*, 0.01 to 0.20 = *Slight agreement*; 0.21 to 0.40 = *Fair agreement*; 0.41 to 0.60 = *Moderate agreement*; 0.61 to 0.80 = *Substantial agreement*; and 0.81 to 0.99 = *Almost perfect agreement*.

Software

Statistical analysis was performed using SPSS Statistical Software Version 22.0 (SPSS®IBM Corporation, Armonk, New York, USA), and AgreeStat (Gwet, 2015).

6.6 Results

6.6.1 Participant characteristics

Of the 59 participants who reported swallowing impairment on Swal-QOL or case history, 38 underwent VFSS. Thirty participants (50%) completed all assessments (Swal-QOL, FDA-2 and VFSS). Sixteen (26.67%) participants completed the Swal-QOL only, 5/60 (8.33%) completed the Swal-QOL and FDA-2 assessment, and 7/60 (11.67%) completed a combination of the Swal-QOL and VFSS. One (1.67%) participant participated in VFSS only after not returning the Swal-QOL, however had previously reported dysphagia on case history (Table 6.1;

Figure 6-1 Venn diagram demonstrating participation across three **assessments**).

6.6.2 Reliability

Intrarater agreement ranged from GAC 0.762 (indicating substantial agreement) for *PAS - Fluid*, to GAC 0.974 ($p<0.05$) (almost perfect agreement) for *PAS - Biscuit*. Interrater reliability ranged from GAC 0.539 (moderate agreement) for *Site of Swallow Reflex - Fluid* to GAC 0.952 (almost perfect agreement) for Lip Function – Fluid (Table 6.2).

Figure 6-1 Venn diagram demonstrating participation across three assessments

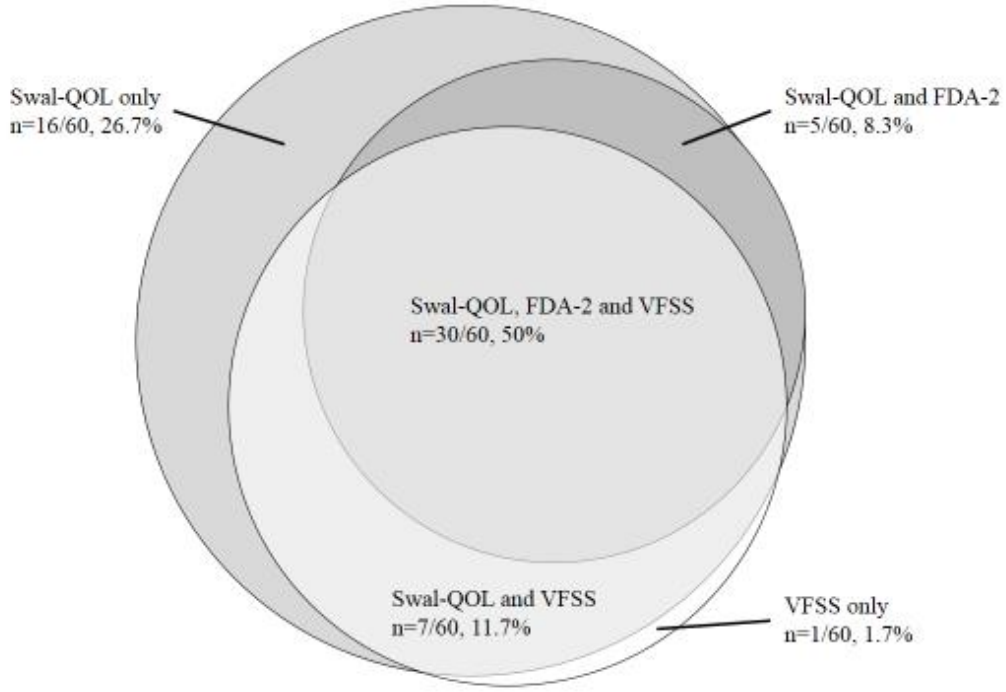


Table 6-1 Demographic and clinical characteristics, and assessment scores of the participant group

Participant ID	Age at disease onset (years)	Disease duration	Gender	GAA1	GAA2	FARS	Total assessment score				
							Swal-QOL	FDA-2	PAS score		
									Fluid	Puree	Biscuit
FA001	13	30.28	Female	706	811	106.5	88	56	1	1	1
FA002	5	35.05	Male	1099	1099	-	60	102	1	2	2
FA003	24	21.78	Male	682	1041	96	94	42	2	1	1
FA004	25	22.62	Female	284	984	78	53	-	1	1	1
FA005	14	15.66	Male	720	720	66	95	64	1	1	1
FA006	15	14.66	Male	720	720	68	85	70	1	1	1
FA007	3	35.03	Male	645	771	127.5	49	115	1	2	1
FA009	14	10.32	Male	471	590	74.5	76	60	2	2	1
FA010	14	15.8	Male	552	552	71.5	80	84	8	2	2
FA011	11	11.15	Female	444	526	70.5	71	56	2	1	1
FA012	14	30.87	Male	650	900	129	66	84	1	1	1
FA013	18	13.4	Female	447	967	102	83	56	2	2	1

FA015	8	31.37	Female	642	1132	136.0	54	94	2	2	1
FA016	28	26.05	Male	606	986	102.5	83	60	1	2	1
FA017	20	29.64	Female	646	1293	115.7	68	76	1	1	1
FA021	7	43.71	Male	780	980	138.5	60	124	8	-	4
FA023	10	16.16	Male	659	822	109.5	54	120	1	-	1
FA024	12	37.34	Male	850	850	-	72	126	8	-	1
FA027	26	25.03	Male	560	989	-	83	80	2	1	1
FA028	19	18.37	Male	476	545	76.5	74	60	4	4	1
FA029	14	17.74	Female	833	835	95.5	84	84	1	8	1
FA032	14	9.84	Male	569	884	77	92	54	1	2	1
FA034	21	17.21	Female	462	462	84.5	21	62	8	1	1
FA036	30	4.74	Female	414	590	63.5	92	34	1	1	1
FA037	3	18.5	Male	800	800	109.5	82	76	2	2	1
FA039	8	25.97	Male	733	943	117.5	100	74	1	1	1
FA040	14	30.21	Male	505	1345	119.5	71	-	1	1	1
FA043	13	14.71	Female	747	875	98.5	98	-	8	1	1

FA044	6	19.52	Male	713	875	111	95	-	8	1	1
FA045	12	10.18	Male	818	818	78	100	-	2	1	1
FA046	18	46.31	Female	489	1207	140	81	-	8	4	8
FA047	17	35.21	Male	589	589	-	68	118	8	4	4
FA048	14	27.04	Male	853	853	-	79	86	4	1	1
FA049	10	7.5	Male	779	932	70	89	39	4	4	1
FA050	7	16.3	Male	998	998	96.5	69	-	1	1	1
FA054	32	16.58	Female	674	803	84	78	56	4	8	4
FA056	16	9.69	Male	630	850	55.5	80	34	1	1	1
FA057	28	15.24	Male	383	942	69.5	-	-	2	1	1
Mean ($\bar{x}$)	15.18	21.77	Female=12	648.11	865.24	95.10	78.87	74.87	3.0	2	1.5
Standard deviation (σ)	7.44	10.32	Male=26	170.53	205.59	24.19	15.03	26.64	2.8	1.8	1.4
Range	3-32	4.74-46.83		284-1099	462-1345	55.5-140	20-93-100	34-126	1-8	1-8	1-8

Swal-QOL: Swallowing Quality of Life Questionnaire; FDA-2: Frenchay Dysarthria Assessment (2nd edition); PAS: Penetration-Aspiration Scale. The optimal score on the Swal-QOL of 220 indicates normal swallowing, with any deviation from this score indicating a degree of impairment. The FDA-2 consists of 26 items and each is scored on a scale from 1 (normal function) to 9 (no function). Therefore FDA-2 scores range from 26 to 234, and scores increase with severity.

Table 6-2 Intrarater and interrater reliability

VFSS rating tool		Consistency	Intrarater reliability (GAC)	Interrater reliability (GAC)
BAS	Lip function	Fluid	0.97**	0.95**
		Puree	0.90**	0.80**
		Biscuit	0.93**	0.87**
	Tongue function	Fluid	0.89**	0.74**
		Puree	0.93**	0.70**
		Biscuit	0.74**	0.67**
	Jaw function	Fluid	0.94**	0.90**
		Puree	0.97**	0.82**
		Biscuit	0.92**	0.79**
	Soft palate elevation	Fluid	0.88**	0.78**
		Puree	0.90**	0.78**
		Biscuit	0.86**	0.76**
	Site of swallow reflex initiation	Fluid	0.80**	0.54**
		Puree	0.88**	0.85**
		Biscuit	0.89**	0.84**
	Aspiration	Fluid	0.90**	0.80**
		Puree	0.89**	0.74**
		Biscuit	0.89**	0.92**
	Residue in the valleculae	Fluid	0.77**	0.75**
		Puree	0.80**	0.66**
		Biscuit	0.77**	0.59**
		Fluid	0.87**	0.63**

	Residue in the pyriform sinuses	Puree	0.89**	0.28**
		Biscuit	0.79**	0.62**
	Pharyngeal function	Fluid	0.83**	0.85**
		Puree	0.88**	0.59**
		Biscuit	0.83**	0.59**
	Cricopharyngeal function	Fluid	0.81**	0.78**
		Puree	0.86**	0.39**
		Biscuit	0.84**	0.72**
PAS		Fluid	0.76**	0.65**
		Puree	0.84**	0.90**
		Biscuit	0.97**	0.64**

** Significant at p<0.01, * significant at p<0.05

6.6.3 VFSS results

6.6.3.1 Penetration and aspiration of the airway

Ten participants (26.3%) aspirated (scoring PAS ≥ 6) on at least one consistency. An additional 3/38 (7.9%) participants demonstrated penetration (PAS score ≥ 3) on at least one consistency. The cumulative total of participants with compromised airway was 13/38 (34.2%). Aspiration occurred most frequently with fluid (8/38 (21.1%) of participants) (Table 6.3).

Table 6-3 Penetration and aspiration (PAS score) (n=38)

	Fluid	Puree	Biscuit
$\bar{x}$	3.03	2.00	1.47
σ	2.76	1.76	1.37
Minimum	1.00	1.00	1.00
Maximum	8.00	8.00	8.00

6.6.3.2 Oral phase parameters

6.6.3.2.1 Lip function

The majority of participants in this study presented with adequate lip function with all consistencies trialled on VFSS (Level 1). Impairment of lip function was observed in 5/38 (13.15%) participants with fluid, 12/36 (33.33%) with puree, and 13/38 (34.2%) with biscuit (Level 2), indicating mild impairment. One participant presented with barium mixture outside of the lips on puree, and 3/38 (7.89%) with biscuit (Table 6.4).

Table 6-4 Lip function (n=38)

Level	Description	Normal range	Fluid		Puree		Biscuit	
			n	%	n	%	n	%
1	No barium mixture observed on or between the lips	91.6%	33	86.8	23	63.9	22	57.9
2	Barium mixture observed between the lips, but remains inside the oral cavity	8.3%	5	13.2	12	33.3	13	34.2
3	Barium mixture observed on the outside of the lips	0%	0	0	1	2.8	3	7.9
4	Barium mixture observed on the chin	0%	0	0	0	0	0	0
X score (σ)			1.13 (0.34)		1.39 (0.55)		1.50 (0.55)	

6.6.3.2.2 Tongue function

Residue in the oral cavity was most evident with biscuit. Twenty-three of the participants (60.53%) demonstrated significant bolus segmentation or had significant residue in the oral cavity following swallow of biscuit. The majority of participants fell in the normal range (Level 1 and 2) with fluid and puree (Table 6.5)

Table 6-5 Tongue function (n=38)

Level	Description	Normal range	Fluid		Puree		Biscuit	
			n	%	n	%	n	%
1	The bolus is propelled into the pharynx in one smooth action and/or with no or minimal coating in the oral cavity after the swallow.	48.3%	20	52.6	5	13.9	0	0
2	The bolus is propelled into the pharynx in 2 or 3 sections and/or coating of the oral structures after the swallow.	51.6%	16	42.1	21	38.3	15	39.5
3	The bolus is propelled into the pharynx in 4 or 5 sections and/or about a quarter of the bolus remains in the oral cavity after the swallow	0%	2	5.3	10	27.8	13	34.2
4	The bolus is propelled into the pharynx in 6 or more sections and/or more than a quarter of the bolus remains in the oral cavity after the swallow.	0%	0	0	0	0	10	26.3
X score (σ)			1.53 (0.60)		2.14 (0.64)		2.87 (0.81)	

6.6.3.2.3 Jaw function

The jaw was observed to remain closed (Level 1) in the majority of participants with all consistencies trialled on VFSS. Jaw movement at the primary point of bolus transfer was observed in 3/38 participants (7.89%) with fluid, 3/36 (8.33%) with puree, and 5/38 (13.16) with biscuit (Table 6.6).

Table 6-6 Jaw function (n=38)

Level	Description	Normal range	Fluid		Puree		Biscuit	
			n	%	n	%	n	%
1	Jaw remains occluded throughout the oral phase	88.5%	34	89.5	32	88.9	31	81.6
2	Jaw movement observed as the tongue begins to push the bolus into the pharynx	11.5%	3	7.9	3	8.3	5	13.2
3	Jaw movement is observed throughout most of the oral phase	0%	1	2.6	1	2.8	2	5.3
4	No functional occlusion is apparent throughout the swallow. The jaw may close briefly but this may be unrelated to the swallow	0%	0	0	0	0	0	0
X score (σ)			1.13 (0.41)		1.14 (0.42)		1.24 (0.54)	

6.6.3.3 Pharyngeal phase parameters

6.6.3.3.1 Soft palate elevation

The majority of participants were within normal limits for soft tissue elevation (*Level 1* and *2*), where the palate elevated above the level of the hard palate forming a peaked or smooth curve. No peaking of the soft palate was observed in 4/38 (5.3%) participants with fluid and biscuit, and 3/36 (8.3%) with puree. Only momentary velopharyngeal closure was observed in 2/37 (5.3%) participants while drinking fluid, 3/36 (8.3%) with puree, and 3/38 (7.9%) with biscuit (Table 6.7).

Table 6-7 Soft palate elevation (n=38)

Level	Description	Normal range	Fluid		Puree		Biscuit	
			n	%	n	%	n	%
1	The soft palate elevates above the level of the hard palate forming a peaked curve	56.5%	18	47.4	18	50.0	17	44.7
2	The soft palate elevates above the level of the hard palate forming a smooth curve	35.5%	14	36.8	13	36.1	14	36.8
3	The soft palate elevates to the level of the hard palate	8.0%	4	10.5	2	5.6	4	10.5
4	The soft palate elevates minimally and/or achieves momentary velar-pharyngeal closure	0%	2	5.3	3	8.3	3	7.9
X score (σ)			1.74 (0.86)		1.72 (0.91)		1.82 (0.93)	

6.6.3.3.2 Reflex initiation

Swallowing reflex initiation was delayed (beyond the faucil pillars) across all consistencies. The swallow was initiated at the level of the valleculae for most participants (Level 3). Ten participants (16.7%) presented with a severe delay in swallow (initiated when the front of the bolus reaches or is past the laryngeal opening and is moving in a vertical direction) with fluid, 6/36 (16.7%) with puree, and 4/38 (13.2%) with biscuit (Table 6.8).

Table 6-8 Reflex initiation (n=38)

Level	Description	Normal range	Fluid		Puree		Biscuit	
			n	%	n	%	n	%
1	The reflex is initiated when the front surface of the bolus reaches the faucil pillars and while the bolus is moving horizontally within the oral cavity	27.0%	0	0	0	0	0	0
2	The reflex is initiated when the front surface of the bolus reaches the back of the tongue and is beginning to move in a vertical direction	51.0%	7	11.7	3	8.3	3	7.9
3	The reflex is initiated when the front surface of the bolus reaches the base of valleculae and the bolus is moving in a vertical direction	21.0%	21	35.0	27	75.0	30	78.9
4	The reflex is initiated when the front surface of the bolus reaches or is past the laryngeal opening and is moving in a vertical direction	1.0%	10	16.7	6	16.7	4	13.2
X score (σ)			3.08 (0.67)		3.08 (0.50)		3.05 (0.46)	

6.6.3.3.3 Aspiration

Aspiration was observed with all consistencies on VFSS, most frequently with fluid (17/38, 44.73%). Penetration was observed in 15/38 (39.5%) participants with fluids, 13/36 (36.1%) with puree, and 3/38 (10.5%) with biscuit. Five participants (13.2%) were noted to aspirate (Level 3) on fluids, 2/36 (5.6%) on puree, 1/38 (2.6%) on biscuit, however this was only trace aspiration viewed as a minor coating. One participant (2.6%) demonstrated severe aspiration on fluids (Level 4) (Table 6.9).

Table 6-9 Aspiration (n=38)

Level	Description	Normal range	Fluid		Puree		Biscuit	
			n	%	n	%	n	%
1	No evidence of penetration or aspiration	99.1%	17	44.7	21	58.3	33	86.8
2	Part of the bolus momentarily penetrates the laryngeal vestibule but is expelled	1.0%	15	39.5	13	36.1	4	10.5
3	Part of the bolus enters and remains in the laryngeal vestibule above the level of the vocal folds, or a small amount of the bolus enters the larynx below the level of the vocal folds (this is viewed as minor coating) but is not expelled	0%	5	13.2	2	5.6	1	2.6
4	Part of the bolus enters the larynx and remains below the level of the vocal folds and/or the trachea	0%	1	2.6	0	0	0	0
X score (σ)			1.74 (0.79)		1.47 (0.61)		1.16 (0.44)	

6.6.3.3.4 Residue in the valleculae

Reside in the valleculae was most evident with biscuit. Twenty-seven (71.05%) participants presented with significant vallecular residue with biscuit (Level 3 or 4). The majority of participants scored within the normal range (Level 1 and 2) for puree and fluid (Table 6.10).

Table 6-10 Residue in the valleculae (n=38)

Level	Description	Normal range	Fluid		Puree		Biscuit	
			n	%	n	%	n	%
1	No coating observed in the valleculae after the swallow	51.0%	19	50.0	3	8.3	4	10.5
2	Coating of the valleculae is observed after the swallow	41.5%	14	36.8	12	33.3	7	18.4
3	Less than 50% of the valleculae are filled with barium mixture after the swallow	6.0%	5	13.2	15	41.7	11	28.9
4	51% or more of the valleculae are filled with barium mixture after the swallow	1.5%	0	0	6	16.7	16	42.1
X score (σ)			1.63 (0.71)		2.67 (0.86)		3.03 (1.03)	

6.6.3.3.5 Residue in the pyriform sinuses

Residue in the pyriform sinuses was most apparent with biscuit, with the majority of participants scoring within the normal range (Level 1 and 2) for puree and fluid. Coating of the valleculae (Level 2) was noted in 12/38 (31.6%) participants following fluid, 16/36 (44.4%) following puree, and 9/38 (23.7%) following biscuit. Only one participant (2.6%) presented with residue in the pyriform sinuses (less than 51%; Level 3) post fluid, compared to 11/36 (30.6%) post puree and 9/38 (23.7%) post biscuit. One participant (2.6%) presented with over 51% of the pyriform sinus filled (Level 4) following swallow of biscuit (Table 6.11).

Table 6-11 Residue in the pyriform sinuses (n=38)

Level	Description	Normal range	Fluid		Puree		Biscuit	
			n	%	n	%	n	%
1	No coating or residue observed in the pyriform sinuses after the swallow	87.0%	25	65.8	9	25.0	10	36.3
2	Coating with barium mixture of the pyriform sinuses observed after the swallow	11.0%	12	31.6	16	44.4	18	47.4
3	Less than 50% of the pyriform sinuses are filled with barium mixture after the swallow	1.5%	1	2.6	11	30.6	9	23.7
4	51% or more of the pyriform sinuses are filled with barium mixture after the swallow	0.0%	0	0	0	0	1	2.6
X score (σ)			1.37 (0.54)		2.06 (0.75)		2.03 (0.79)	

6.6.3.3.6 Pharyngeal function

Pharyngeal dysfunction was more severe with solid consistencies. Over half (25/38, or 65.79%) of the participants were able to clear fluids from the pharynx with no coating evident

post swallow (Level 1), compared to 6/36 (16.7%) following puree, and 5/38 (13.2%) following biscuit. Coating of the pharyngeal structures (Level 2) was observed following swallow in 10/38 (26.3%) participants post fluid, 13/36 (36.1%) post puree, and 16/38 (42.1%) post biscuit. The bolus was observed to move through the pharynx as a column, required multiple swallows to clear, or left minimal residue after the swallow (Level 3) in 3/38 (7.9%) participants post fluid, 13/36 (36.1%) post puree, and 13/38 (34.2%) post biscuit. Four participants presented with pooled residue in the pharynx after the swallow, or required multiple swallows to shift the bolus through the pharynx (Level 4) post puree (11.1%) and biscuit (10.5%) (Table 6.12).

Table 6-12 Pharyngeal function (n=38)

Level	Description	Normal range	Fluid		Puree		Biscuit	
			n	%	n	%	n	%
1	The bolus moves through the pharynx in an ovoid or mouse shape and/or no coating of the pharyngeal structures after the swallow	90.5%	25	65.8	6	16.7	5	13.2
2	The bolus moves through the pharynx in an elongated sausage shape and/or coating of pharyngeal structures after the swallow	9.5%	10	26.3	13	36.1	16	42.1
3	The bolus moves through the pharynx as a column and/or requires 2 swallows to clear and/or minimal residue after the swallow	0.0%	3	7.9	13	36.1	13	34.2
4	The bolus is fragmented as it moves through the pharynx and/or requires 3 or more swallows to clear and/or pooled residue after the swallow	0.0%	0	0	4	11.1	4	10.5
X score (σ)			1.42 (0.64)		2.42 (0.91)		2.42 (0.86)	

6.6.3.3.7 Cricopharyngeal function

No residue was observed above the cricopharyngeus (Level 1) in 23/38 (60.5%) participants post fluid, 5/36 (13.9%) post puree, and 5/38 (13.2%) post biscuit. Coating of the cricopharyngeal lumen was noted after the swallow (Level 2) in 11/38 (28.9%) participants post fluid, 14/36 (38.9%) post puree, and 14/38 (36.8%) post biscuit. Coating of the lumen and a small amount of barium (Level 3) was observed in 4/38 (10.5%) participants post fluid, 13/36 (36.1%) post puree, and 12/38 (31.6%) post biscuit. Pooling of residue directly above the cricopharyngeus after the swallow (Level 4) occurred in 4/38 (11.1%) participants following puree and 7/38 (18.4%) post biscuit (Table 6.13).

Table 6-13 Cricopharyngeal function (n=38)

Level	Description	Normal range	Fluid		Puree		Biscuit	
			n	%	n	%	n	%
1	No residue observed in the cricopharyngeal region after the swallow	77.5%	23	60.5	5	13.9	5	13.2
2	Coating of the cricopharyngeal lumen after the swallow	21.0%	11	28.9	14	38.9	14	36.8
3	Coating of the cricopharyngeal lumen and a small amount of barium directly above cricopharyngeus after the swallow	1.5%	4	10.5	13	36.1	12	31.6
4	Coating of the cricopharyngeal lumen and a pooling of barium residue directly above cricopharyngeus after the swallow	0.0%	0	0	4	11.1	7	18.4
X score (σ)			1.50 (0.69)		2.44 (0.88)		2.55 (0.95)	

6.6.4 Dysphagia severity

DOSS scores ranged from 6 (within functional limits/modified independence) to 2 (moderately severe dysphagia). Three participants (7.9%) received a DOSS score of 6, whereby the participant presented with a functional swallow however may present with mild oral or pharyngeal dysphagia (excluding aspiration or require extra time for a meal. The majority of participants (32/28, 84.2%) presented with mild, mild-moderate, or moderate dysphagia (scoring 5, 4, or 3 on the DOSS). Fifteen participants (39.5%) presented with mild dysphagia (DOSS score 5), defined by the individual requiring distant supervision or one diet consistency restricted. Individuals with mild dysphagia may also present with aspiration of thin fluids with a strong reflexive cough. Mild-moderate dysphagia (DOSS score 4) was recorded for 13/38 participants (34.2%) characterised by intermittent supervision/cueing and modified consistencies of diet and/or fluid. The individual may also present with oral and/or pharyngeal residue and requires prompting to effectively clear. Four participants (10.5%) presented with moderate dysphagia, whereby they require total assistance with eating and drinking, strategies, and two of more diet consistencies are restricted. Three participants (7.9%) in this study presented with moderately-severe dysphagia (DOSS score 3), defined by a requirement for maximum assistance and use of swallowing strategies (Figure 6-2 Distribution of DOSS scores (n=38)).

Figure 6-2 Distribution of DOSS scores (n=38)

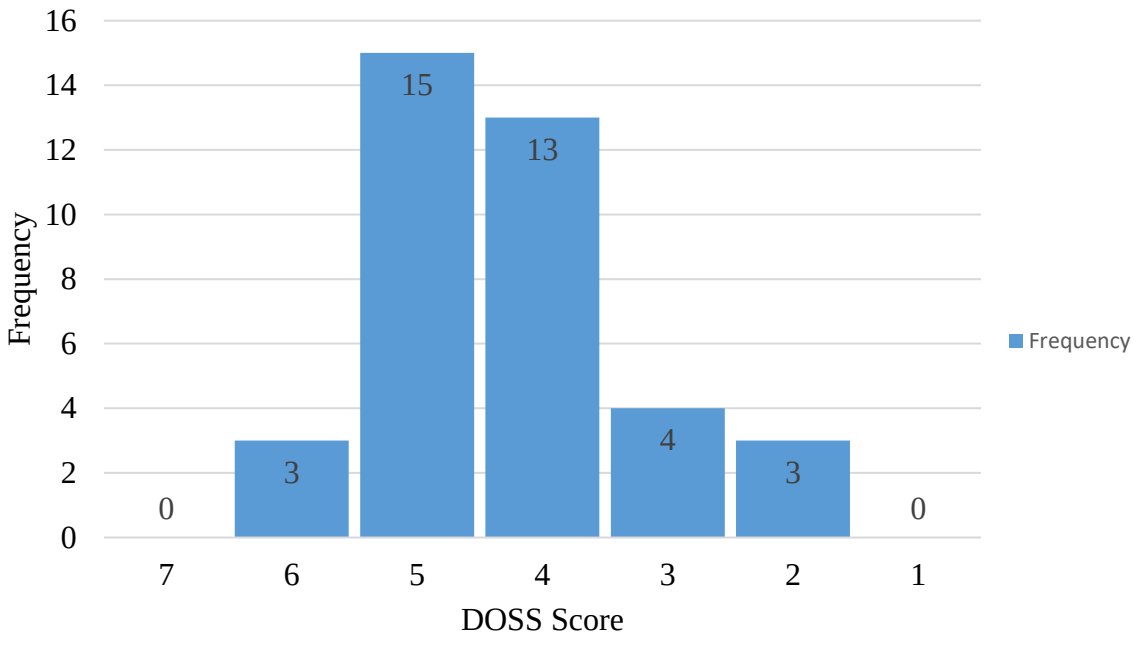


Figure 6-3 VFSS of a 50.71 year old male with FRDA

Age at onset - 7 years, disease duration – 43.71 years, FARS score - 138.5; a) Delayed pharyngeal swallow with unmodified fluids, and b) pharyngeal residue post swallow of dry biscuit

a) b)

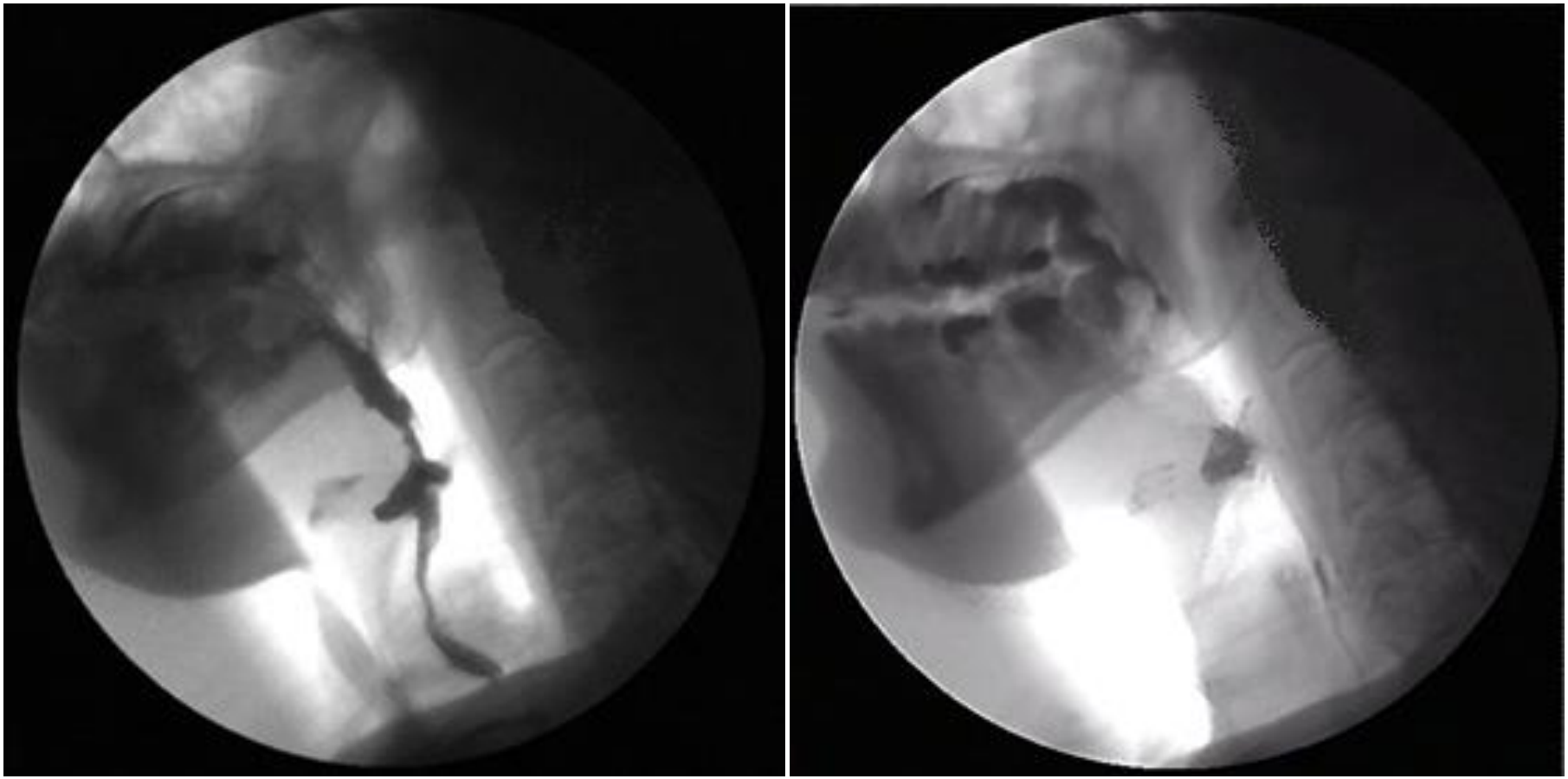
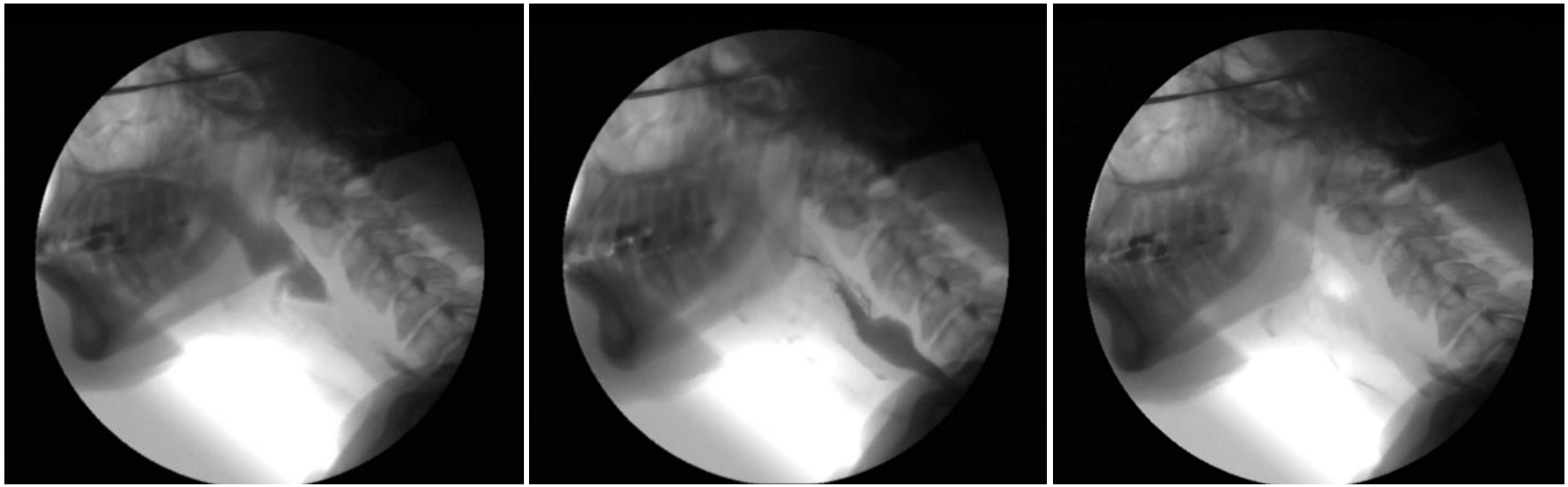


Figure 6-4 VFSS of a 52.21 year old female with FRDA

Age at onset - 17 years, disease duration – 35.21 years, no FARS score; a) Swallow initiation (epiglottic deflection, laryngeal excursion) occurring once the bolus has passed beyond the laryngeal opening, with entry of barium into the airway; b) The bolus passing through the upper oesophageal sphincter and contrast observed passing below the vocal folds; and c) After the swallow is completed, trace coating of barium is evident on the anterior surface of the trachea, with no cough initiated

a) b) c)



6.6.5 Relationships between swallowing function and FRDA clinical parameters

Penetration/aspiration of biscuit correlated significantly with age at assessment ($\rho = 0.41$, $p<0.05$) and disease duration ($\rho = 0.38$, $p<0.05$). No significant correlations were observed between FRDA clinical parameters and aspiration of fluid or puree. Deficits in the oral phase parameters of the BAS correlated with FARS score (lip function with fluid: $\rho = 0.48$, $p<0.01$; jaw function with biscuit:, $\rho = 0.38$, $p<0.05$), age at assessment (lip function with fluid: $\rho = 0.44$, $p<0.01$; jaw function with biscuit: $\rho = 0.34$, $p<0.05$), and disease duration (lip function with fluid: $\rho = 0.58$, $p<0.01$; jaw function with puree, $\rho = 0.44$, $p<0.01$; and biscuit, $\rho = 0.46$, $p<0.01$). There was a significant relationship between disease duration and pharyngeal phase deficits with solid food (biscuit) (reflex initiation $\rho = 0.43$, $p<0.01$; Aspiration $\rho = 0.45$, $p<0.01$; valleculae $\rho = 0.35$, $p<0.05$; pharyngeal $\rho = 0.33$, <0.05). Disease duration correlated with soft palate elevation ($\rho=0.50$, $p<0.01$), reflex initiation ($\rho = 0.43$, $p<0.01$), aspiration ($\rho = 0.45$, $p<0.01$), vallecular residue ($\rho = 0.35$, $p<0.05$), and pharyngeal function ($\rho = 0.33$, $p<0.05$). GAA1 length positively correlated with vallecular residue of biscuit ($\rho = 0.42$, $p<0.01$). GAA2 length positively correlated with vallecular ($\rho = 0.35$, $p<0.05$) and pharyngeal residue ($\rho = 0.45$, $p<0.01$) (Table 6.14).

Table 6-14 Correlations between FRDA, and the PAS and DOSS

	PAS score			DOSS
	Fluid	Puree	Biscuit	
GAA1	-0.02	0.03	0.04	-0.12
GAA2	-0.20	-0.12	0.03	0.01
FARS	0.06	0.10	0.21	-0.37*
Age at disease onset	0.01	-0.03	0.04	0.12
Age at assessment	0.11	0.09	0.41*	-0.34*
Disease duration	0.12	0.16	0.38*	-0.48**

PAS: Penetration-Aspiration Scale; DOSS: Dysphagia Outcome Severity Scale; **significant at $p<0.01$, *significant at $p<0.05$

Table 6-15 Correlations between FRDA and oral phase swallowing impairment

FRDA clinical parameters	Lip function			Tongue function			Jaw function			Soft palate			Reflex		
	Fluid	Puree	Biscuit	Fluid	Puree	Biscuit	Fluid	Puree	Biscuit	Fluid	Puree	Biscuit	Fluid	Puree	Biscuit
GAA1	0.07	-0.32	-0.11	-0.09	0.03	0.14	-0.11	0.12	0.00	-0.14	-0.17	-0.07	-0.08	-0.14	-0.01
GAA2	-0.01	0.08	0.16	-0.18	0.05	0.11	-0.02	0.08	0.09	0.16	0.17	0.21	0.04	-0.19	0.15
FARS	0.48**	0.20	0.13	0.18	0.03	0.26	0.17	0.31	0.38*	0.45**	.406*	0.46**	0.21	0.05	0.42*
Age at onset	-0.17	0.18	0.01	-0.05	0.00	-0.28	0.00	-0.16	-0.12	-0.14	-0.10	-0.20	-0.05	-0.02	-0.04
Age at assessment	0.44**	0.31	0.25	0.10	0.11	0.06	0.14	0.28	0.34*	0.27	0.30	0.31	0.18	0.06	0.34*
Disease duration	0.58**	0.19	0.20	0.19	0.11	0.26	0.17	0.44**	0.46**	0.42**	0.45**	0.50**	0.21	0.13	0.43**

**significant at p<0.0.1, *significant at p<0.05

Table 6-16 Correlations between FRDA and pharyngeal phase swallowing impairment

FRDA clinical parameters	Aspiration			Valleculae			Pyriform			Pharyngeal			Cricopharyngeal		
	F	P	B	F	P	B	F	P	B	F	P	B	F	P	B
GAA1	-0.07	0.08	0.10	-0.15	0.03	0.42**	-0.19	-0.20	0.08	-0.21	0.00	0.18	0.00	0.00	0.18
GAA2	-0.16	-0.03	0.14	0.12	0.09	0.35*	0.15	0.13	0.26	0.05	0.37*	0.45**	0.04	0.11	0.21
FARS	0.11	0.18	0.32	0.14	0.03	0.30	0.06	-0.01	0.17	0.17	0.16	0.29	0.07	0.00	0.25
Age at onset	0.01	-0.08	0.02	0.06	0.03	-0.30	0.00	0.14	-0.21	-0.02	-0.17	-0.30	-0.12	-0.06	-0.24
Age at assessment	0.14	0.09	0.46**	0.33*	0.23	0.14	0.19	0.26	0.08	0.31	0.10	0.14	0.17	0.08	0.11
Disease duration	0.16	0.18	0.45**	0.26	0.27	0.35*	0.14	0.22	0.24	0.29	0.22	0.33*	0.21	0.12	0.25

**significant at p<0.0.1, *significant at p<0.05, F-Fluid, P-Puree, B-Biscuit

Table 6-17 Correlations between significant airway penetration and/or aspiration and swallowing-related QOL

		Burden	Eating desire	Eating duration	Symptom frequency	Food selection	Communication	Fear	Mental health	Social	Fatigue	Sleep	Total Swal-QOL score
PAS score	Fluid	-0.06	0.25	-0.16	-0.10	0.01	-0.10	0.06	-0.05	-0.16	0.06	-0.11	-0.06
	Puree	-0.16	0.04	-0.11	-0.15	0.15	0.01	-0.10	-0.16	-0.04	-0.24	-0.46**	-0.21
	Biscuit	-0.28	0.26	-0.44**	-0.24	-0.13	-0.18	-0.11	-0.10	-0.28	0.11	-0.28	-0.26

**significant at p<0.0.1, *significant at p<0.05

Table 6-18 Correlations between significant airway penetration and/or aspiration and oromotor function

		Reflexes	Respiration	Lips	Palate	Laryngeal	Tongue	Intelligibility	Total FDA-2 score
PAS score	Fluid	0.34	0.10	0.17	0.25	0.08	-0.03	0.33	0.19
	Puree	0.24	0.12	0.23	-0.01	0.13	0.32	0.26	0.18
	Biscuit	0.33	0.17	0.33	0.15	0.29	0.36	0.33	0.33

**significant at p<0.01, *significant at p<0.05

6.7 Predictors of significant airway penetration and/or aspiration in FRDA

6.7.1 Logistic regression analysis

Direct logistic regression was performed to assess the predictive ability of the clinical and behavioural data from Study 1 - Swallowing-related quality of life in individuals with Friedreich ataxia and Study 2 – Clinical bedside examination of oromotor function and swallowing in FRDA using a standardised assessment on the occurrence of significant airway entry when swallowing. For logistic regression, the sample was dichotomised into two groups: 1) those with adequate airway protection (PAS scores all < 3) (n=25), and 2) those who demonstrated penetration/aspiration of the airway on any consistency (at least one PAS score > 3) (n=13). The independent variables included GAA2, FDA-2 Reflexes, and FDA-2 Intelligibility, which were determined by running logistic regression for each independent variable and identifying the independent variables that most related to the model (Table 6-20 Logistic regression between significant airway entry (PAS > 3) and independent variable).

The full model containing all independent variables was statistically significant, $X^2(3, N=30) =8.971$ (p=0.03), indicating that the model was able to differentiate between participants who demonstrated penetration and/or aspiration on at least one consistency and those who did not. The model as a whole explained between 25.8% (Cox and Snell R square) and 35.9% (Nagelkerke R Square) of cases, and correctly classified 76.7% of cases. Sensitivity was 60% and specificity was 85%, indicating a tendency towards under-prediction. None of these variables made a unique significant contribution to the model (Table 6.19). The strongest predictor of penetration/aspiration in individuals with FRDA was FDA-2 Reflexes, with an odds ratio of 1.260.

Table 6-19 Logistic regression predicting likelihood of airway entry of barium

Variables	B	Wald	df	p	Odds ratio	95% confidence interval for odds ratio	
						Lower	Upper
GAA2	-0.00	2.60	1	0.11	0.99	0.99	1.00
FDA-2 Reflexes	0.23	1.26	1	0.26	1.26	0.84	1.89
FDA-2 Intelligibility	0.07	0.23	1	0.63	1.07	0.81	1.42

Table 6-20 Logistic regression between significant airway entry (PAS > 3) and independent variables

		Equation	Cox and Snell R square	Nagelkerke R squared	Whole model	Wald	Sig
FRDA clinical parameters	GAA1	X2(1, N=38)=0.57 (p=0.45)	0.02	0.02	63.2%	0.56	0.45
	GAA2	X2(1, N=38)=2.33 (p=0.13)	0.06	0.08	68.4%	2.13	0.15
	FARS	X2(1, N=38)=0.09 (p=0.76)	0.00	0.00	69.7%	0.09	0.76
	Age at disease onset	X2(1, N=38)= 0.00 (p=0.98)	0.00	0.00	65.8%	0.00	0.99
	Disease duration	X2(1, N=38)= 1.32 (p=0.25)	0.03	0.05	71.1%	1.29	0.26
Swal-QOL	Total score	X2(1, N=37)= 0.20 (p=0.66)	0.01	0.01	64.9%	0.20	0.66
	Burden	X2(1, N=37)= 1.20 (p=0.62)	0.01	0.01	64.9%	0.26	0.61
	Eating desire	X2(1, N=37)=0.02 (p=0.88)	0.00	0.00	64.9%	0.02	0.89
	Eating duration	X2(1, N=37)= 0.42 (p=0.52)	0.01	0.02	64.9%	0.42	0.52
	Symptom frequency	X2(1, N=37)=0.53 (p=0.47)	0.01	0.35	67.6%	0.53	0.47
	Food selection	X2(1, N=37)=0.27 (p=0.87)	0.00	0.00	64.9%	0.03	0.87
	Communication	X2(1, N=37)= 0.00 (p=0.97)	0.00	0.00	64.9%	0.00	0.97
	Fear	X2(1, N=37)= 0.00 (p=0.78)	0.00	0.00	64.9%	0.08	0.78

	Mental health	X2(1, N=37)= 0.02 (p=0.90)	0.00	0.00	64.9%	0.02	0.90
	Social	X2(1, N=38)= 0.12 (p=0.73)	0.00	0.00	64.9%	0.12	0.73
	Fatigue	X2(1, N=38)=0.84 (p=0.77)	0.00	0.00	64.9%	0.08	0.77
	Sleep	X2(1, N=38)= 1.28 (p=0.26)	0.03	0.05	64.9%	0.26	0.84
FDA-2	Total score	X2(1, N=30)= 1.78 (p=0.18)	0.06	0.08	70.0%	1.70	0.19
	Reflexes	X2(1, N=30)=5.98 (p=0.01*)	0.18	0.25	80.0%	4.59	0.03*
	Respiration	X2(1, N=30)= 1.36 (p=0.24)	0.04	0.06	73.3%	1.31	0.25
	Lips	X2(1, N=30)= 2.88 (p=0.09)	0.09	0.13	73.3%	2.56	0.11
	Palate	X2(1, N=30)= 1.11 (p=0.29)	0.04	0.05	70.0%	1.05	0.31
	Laryngeal	X2(1, N=30)= 0.22 (p=0.64)	0.01	0.01	66.7%	0.22	0.64
	Tongue	X2(1, N=30)= 0.30 (p=0.58)	0.01	0.01	66.7%	0.30	0.59
	Intelligibility	X2(1, N=30)= 3.11 (p=0.08)	0.10	0.14	60.0%	2.82	0.09

**significant at p<0.0.1, *significant at p<0.05

6.7.2 Multiple regression analysis

A standard multiple regression was performed between the PAS score for each consistency as the dependent variable and GAA1, GAA2, age at disease onset, Swal-QOL total score, and FDA-2 total score as the independent variables. FARS and age at assessment were excluded from regression analysis on the basis of collinearity ($r>0.7$ and tolerance values <0.1).

Fluid

R was not significant, $F(6, 23) = 1.55$, $p=0.21$, with R^2 at 0.29. None of the independent variables reached statistical significance. The adjusted R^2 value of 0.10 indicated that only 10% of the variance can be predicted by the model (Table 6.21).

Puree

R was not significant, $F(6, 21) = 0.50$, $p=0.81$, with R^2 at 0.12. None of the independent variables reached statistical significance. The adjusted R^2 value was -0.13 meaning 0% can be explained by this model (Table 6.22).

Biscuit

R was not significant, $F(6, 23) = 2.30$, $p=0.69$, with R^2 at 0.40. None of the independent variables reached statistical significance. The adjusted R^2 value of 0.21 indicated that only 21% of the variance can be predicted by the model (Table 6.23).

6.8 Post hoc evaluation of incidence of chest infections in clinical cohort

To explore the clinical significance of aspiration in FRDA, a retrospective audit was conducted of clinical reports to determine the incidence of chest infection in individuals with FRDA. Clinical data from 587 Speech Pathology reports (159 patients attending the Friedreich ataxia Clinic between the years 2005 to 2015) were reviewed. Chest infection were reported 27/587 reports, equating to an incidence of 4.7%.

Table 6.21 Multiple regression - Penetration/aspiration of fluid

	PAS fluid (DV)	GAA 1	GAA2	Age at disease onset	Disease duration	Swal-QOL total score	FDA-2 total score	B	Beta	sr^2
GAA 1	-0.00							-0.00	-0.16	0.01
GAA 2	-0.22	0.21						-0.01	-0.36	0.08
Age at disease onset	-0.06	-0.58	-0.04					0.04	0.12	0.01
Disease duration	0.29	0.20	0.46	-0.21				0.05	0.18	0.71
Swal-QOL total score	-0.15	0.20	0.10	0.06	-0.28			0.02	0.22	0.02
FDA-2 total score	0.37	0.42	0.14	-0.50	0.76	-0.48		0.05	0.52	0.04
							Intercept = -0.57			
$\bar{x}$	3.03	648.11	865.24	15.18	21.76	179.51	74.87	R^2 = 0.29		
σ	2.76	170.53	205.59	7.44	10.28	28.89	26.65	Adjusted R^2 = 0.10		
								R=0.54		

Table 6.22 Multiple regression - Penetration/aspiration of puree

	PAS fluid (DV)	GAA 1	GAA2	Age at disease onset	Disease duration	Swal-QOL total score	FDA-2 total score	B	Beta	sr^2
GAA 1	0.10							0.00	0.26	0.03
GAA 2	-0.09	0.21						-0.00	-0.16	0.02
Age at disease onset	0.16	-0.58	-0.04					0.10	0.41	0.09
Disease duration	0.05	0.20	0.46	-0.21				0.00	0.00	0.00
Swal-QOL total score	0.01	0.20	0.10	0.06	-0.28			0.00	0.05	0.00
FDA-2 total score	0.080	0.42	0.14	-0.50	0.76	-0.48		0.01	0.21	0.01
							Intercept= -1.70			
$\bar{x}$	2.00	648.11	865.24	15.18	21.76	179.51	74.87	R^2 = 0.12		
σ	1.76	170.53	205.59	7.44	10.28	28.89	26.65	Adjusted R^2 = -0.13		
								R=0.35		

Table 6.23 Multiple regression – Penetration/aspiration of biscuit

	PAS biscuit (DV)	GAA 1	GAA2	Age at disease onset	Disease duration	Swal-QOL total score	FDA-2 total score	B	Beta	sr^2
GAA 1	-0.05							-0.00	-0.21	0.02
GAA 2	0.16	0.21						0.00	-0.07	0.00
Age at disease onset	0.11	-0.58	-0.04					0.05	0.26	0.04
Disease duration	0.52	0.20	0.46	-0.21				0.06	0.42	0.04
Swal-QOL total score	-0.05	0.20	0.10	0.06	-0.28			0.01	0.30	0.05
FDA-2 total score	0.36	0.42	0.14	-0.50	0.76	-0.48		0.02	0.41	0.03
							Intercept=-1.49			
$\bar{x}$	1.47	648.11	865.24	15.18	21.76	179.51	74.87	$R^2 = 0.40$		
σ	1.37	170.53	205.59	7.44	10.28	28.89	26.65	Adjusted $R^2 = 0.21$		
								R= 0.61		

6.9 Discussion

This is the first study to systematically describe swallowing function in FRDA and determine the relationships between dysphagia and clinical and behavioural data. The swallowing function of 38 individuals with FRDA who had previously reported dysphagia symptoms was considered using VFSS, the current clinical standard of assessment. All participants in this study presented with oropharyngeal dysphagia on VFSS. Delayed pharyngeal swallowing reflex was the most apposite factor of FRDA-related dysphagia as well as lingual dysfunction and the presence of residue in the pharyngeal structures, supporting the primary hypothesis. Significant entry of barium into the airway was observed in 34.2% of the cohort, and aspiration in 26.32%, supporting the second hypothesis. Dysphagia (including site specific characteristics and overall dysphagia severity) in FRDA appears to be progressive given significant correlational relationships between oropharyngeal dysphagia and disease duration and severity. All of those who aspirated did so silently, and no reliable predictors of aspiration were found, highlighting the need for instrumental analysis for accurate identification of aspiration in this population.

6.9.1 Prevalence, characteristics and site-specific characteristics of FRDA-related dysphagia

The clinical signs of dysphagia in FRDA have previously been described by means of observation and subjective patient reports and include coughing/choking on dry, crumbly or solid foods (reported in 14/36, or 38.89 % of participants), oral residue (1/36, or 2.78% of participants) and nasal regurgitation (1/36, or 2.78% of participants) (Vogel et al., 2014). In the current study the most germane feature of dysphagia was pharyngeal phase dysfunction, with 100% (38/38) of participants presenting with pharyngeal phase deficits on at least one consistency trialled on VFSS. A delay in swallowing initiation was most severe with fluids, whilst difficulty clearing residue from the pharynx was most prevalent in solids (puree and biscuit). The presence of residue in the valleculae and pyriform sinuses (observed on at least one consistency in all participants) is indicative of reduced laryngeal excursion, epiglottic deflection, and pharyngeal contraction, whilst cricopharyngeal pooling is indicative of disturbed relaxation of the cricopharyngeus (Scott, 1999). Impairments of the pharyngeal phase of swallowing co-varied with disease severity and duration, particularly with harder food substances. This information will assist to inform dysphagia management as the disease progresses and supports evidence of individuals with FRDA requiring softer foods as the disease progresses (Corben et al., 2014).

Vogel and colleagues (2014) reported coughing and choking during swallowing in individuals with FRDA, a sign of pharyngeal phase dysfunction and possible aspiration. In the present study, coughing and choking was not observed on VFSS in response to barium entry into the airway, however 51/59 (86.44%) participants reported coughing with oral intake in the swallowing related QOL study described in Chapter 4. Aspiration observed on VFSS did not significantly correlate with subjective reports of dysphagia symptoms on the Swal-QOL. These data suggest the presence or absence of a cough on bedside examination of swallowing is not a reliable indicator of aspiration in individuals with FRDA. Inability to recognise and address silent aspiration can result in serious respiratory complications, necessitating instrumental evaluation of swallowing in all cases where aspiration is suspected.

6.9.2 Prevalence of penetration and aspiration in FRDA

A major goal of this study was to determine the frequency of penetration and aspiration in individuals with FRDA. The prevalence of aspiration of fluids amongst healthy individuals reported in the literature is 0%, and 1% for penetration (n=95) (Robbins et al., 1999). In individuals with FRDA, aspiration of at least one consistency was recorded in 26.3% of participants, and penetration in a further 7.9%; significantly higher than that of the healthy population. Additionally, all individuals with FRDA who aspirated did so silently. In this study, aspiration was observed in trace amounts, and thus it is possible the amount of aspirated material was not enough to elicit a reflexive cough (Leder, Suiter, & Green, 2011). Given the BAS and PAS do not allow for quantification of the aspirated bolus, it is possible these factors may have biased the data, and may explain the discrepancy seen between subjective reports of coughing with food and drinking, and the silent aspiration on VFSS.

6.9.3 Predictors of significant airway compromise in FRDA

No significant differences were found between the clinical characteristics of individuals with FRDA who aspirated, and those who did not. Further comparisons made between the Swal-QOL and FDA-2 (Study 1 - Swallowing-related quality of life in individuals with Friedreich ataxia and 5) did not yield any significant differences. Therefore, attempts to find clinically meaningful thresholds within the behavioural and self-report assessments to predict penetration or aspiration did not yield any sensitive markers of aspiration in individuals with FRDA. The predictability of aspiration in other neurodegenerative populations is variable. A clinical neurological examination is reported to predict aspiration in individuals with myasthenia gravis (n=20) with 71% sensitivity and 77% specificity (Koopman et al., 2004),

whilst in the ischemic stroke population (n=96), objective measures of cough are reported to predict aspiration with 82-91% sensitivity and 81-92% specificity (Hammond et al., 2009). Tohara and colleagues (2003) reported a combination of three non-videofluorographic swallowing assessments to have a sensitivity of 90% and specificity of 71% in predicting aspiration in a heterogeneous group of individuals (n=63). These figures demonstrate a trend of over and under-prediction of aspiration in these cohorts, which may also be applicable to FRDA.

6.9.4 FRDA compared to other neurodegenerative conditions

The presence of oral and pharyngeal dysphagia in FRDA is unsurprising given the prevalence of dysphagia reported in other similar yet wholly different conditions. In ALS, dysphagia is reported to affect between 21.1% (Atsuta et al., 2009) to 65.2% (Tomik, Tomik, Partyka, Skladzien, & Szczudlik, 2007) of individuals, and is related to the bulbar onset variant of the disease (Ruoppolo et al., 2013). Similarly, dysphagia is reported in HD (Heemskerk & Roos, 2011), MS (Guan, Wang, Huang, & Meng, 2015), and PD (Kalf, De Swart, Bloem, & Munneke, 2012). As previously discussed in Chapter 3, dysphagia is known to exists in the HASs (Nilsson, Ekberg, Olsson, & Hindfelt, 1996; Vogel et al., 2014; Vogel, Fendel, Brubacher, Chan & Maule, 2015), with oral and pharyngeal phase dysphagia (delayed pharyngeal swallow) being reported in a heterogeneous sample of 8 individuals with a form of hereditary ataxia. The majority of research relating to dysphagia in neurodegenerative disease is retrospective, or based on subjective questionnaires only. Detailed studies of dysphagia secondary to neurodegeneration using VFSS are sparse, and thus comparisons between dysphagia and airway compromise in FRDA and other hereditary ataxia or cerebellar disturbance is problematic. Vogel and colleagues (2015a) retrospectively reported on 24 individuals presenting to a tertiary institution in Melbourne over a two and a half year period. Of the 24 participants, 13 presented with SCA (types SCA1, SCA2, SCA3, and SCA17) and 11 with multiple system atrophy-cerebellar type (MSA-C). Data pertaining to swallowing from medical chart reports, reports by treating physicians, and VFSS where available, were collated and reviewed to determine the dysphagia profile of both groups. The results of this study reveal two distinct and disease-specific dysphagia profiles. Deficits in the oral preparatory phase of swallowing (lifting food/drink to the mouth and self-feeding) were more prevalent in SCA (n=8/13, 61.54%) compared to MSA-C (n=2/11, 18.18%), whilst secretion management issues (xerostomia, thick saliva, choking/coughing with secretions) were reported by individuals with SCA but not MSA-C. Oral phase deficits were experienced

by both groups and included prolonged oral preparation of a bolus, oral residue and delayed swallowing reflex. Traditional signs of material entering the airway, including coughing/choking when eating and drinking were reported by the majority of individuals with SCA (10/13), but not reported in MSA-C. Silent aspiration was reported in one individual with SCA and no individuals with MSA-C.

Whilst there are similarities, the results of the present study reveal a unique dysphagia profile in FRDA compared to SCA and MSA-C. Drooling (excess secretions) is experienced more frequently in FRDA (36/59, 61%, as reported on the Swal-QOL) compared to SCA (1/13, 7.7%) and was unreported on MSA-C (0/11, 0%). Further, thick saliva was reported by 32/59 (54.2%) of individuals with FRDA (on the Swal-QOL) compared to 4/13 (30.8%) with SCA and 0/11 (0%) with MSA-C. The sample sizes and methodology included in the present study and the study by Vogel and colleagues (2015a) are significantly different, these data suggest that secretion management issues are more prevalent and expected as a consequence of FRDA compared to other hereditary ataxia syndromes, with the exception of SCA (Vogel et al., 2015a). In the oral phase of swallowing, reduced oral clearance and oral residue post swallow appears consistently in individuals with FRDA (all participants in the present study presented with diminished lingual function manifesting in oral residue post swallow with biscuit) and appears a hallmark feature of the disease, whilst is only experienced sporadically by individuals with SCA and MSA-C (Vogel et al., 2015a). Residue in the valleculae and pharyngeal structures appears a feature of FRDA more so than in other hereditary ataxia syndromes such as SCA or MSA-C (Vogel et al., 2015a). The presence of residue in the pharyngeal structures seen in FRDA may be exacerbated by diminished lingual function known to exist in FRDA (Folker et al., 2010; Folker et al., 2011) affecting propulsion of material towards the pharynx. This, coupled with reduced laryngeal excursion (upward and forward movement) likely impacts on cricopharyngeal opening and deflection of the epiglottis. The presence of residue in the pharyngeal structures is known to increase the risk of post-swallow aspiration (Molfenter & Steele, 2013), which should be considered in the clinical management of individuals with FRDA.

A pertinent finding in this study was the existence of airway compromise (penetration and aspiration), and silent aspiration in FRDA. Aspiration and penetration of the laryngeal vestibule were reported in SCA (3/13, 23.1%) and MSA-C (5/11, 45.4%) (Vogel et al., 2015a), however silent aspiration is not a reported feature of these conditions. In ataxia-telangiectasia (AT), aspiration is reported to occur in 27% of individuals (n=14/51), and silent aspiration in 71% (10/14) of those known to aspirate (Lefton-Greif et al., 2000). Silent aspiration has also been a reported feature of ALS with a prevalence of 20.4% (n=10/49) (Ruoppolo et al., 2013).

6.9.5 Clinical implications, recommendations and future direction

Swallowing function and swallowing perception do not correlate in individuals with FRDA, and therefore open-ended questions enquiring about swallowing function during a scheduled clinical visit may not be considered valid in FRDA. More informed specific questioning pertaining to swallowing function may be a reliable indicator, however it is recommended clinicians screen individuals with FRDA for dysphagia using a standardised questionnaire such as the Swal-QOL. Results of the Swal-QOL will inform the clinician on the impact dysphagia may have on the QOL of the individual, and this information should be used to guide management and rehabilitation of swallowing function. Furthermore, a bedside swallowing assessment, and a judgement of aspiration based on the presence or absence of a cough on bedside assessment is not reliable given significant silent aspiration in the FRDA population. Instrumental analysis remains the only objective way to identify aspiration in this population, however recommendations made should consider the significant limitations of VFSS. The management of FRDA-related dysphagia should be guided and informed via collaboration between the Speech Pathologist, Neurologist, the wider treating team, and the patient, to address the physical and psychosocial impacts of the condition.

Whilst silent aspiration was observed in more than a quarter of participants, the clinical implications of FRDA-related aspiration remain unclear. Pneumonia is reported to account for almost 10% of deaths in the FRDA population (Tsou et al., 2011), however data pertaining to the frequency of aspiration-related pneumonia in the FRDA population is lacking. Anecdotal evidence and expert opinion from one centre only suggests aspiration-related pneumonia is uncommon in the FRDA population, however an important next step in this research would be to determine the causal relationship, if any, between dysphagia with concomitant aspiration and the presence of aspiration-related pneumonia. To further investigate the clinical relevance of aspiration in FRDA we conducted a post hoc analysis to

establish an incidence of chest infection in the FRDA population. A retrospective audit of the medical files of individuals with FRDA revealed a chest infection incidence of 4.6%. This figure is evidently less than the prevalence of aspiration (over 25%) observed in this study and the reported 10% of deaths in FRDA accountable to pneumonia (Tsou et al., 2011). Thus, whilst aspiration is common in this population it does not always translate into clinical presentation.

It is likely dysphagia in FRDA is a consequence of mistiming and incoordination of the swallow arising from cerebellar and spinocerebellar degeneration, and is exacerbated by spasticity and weakness. Deficits observed during the oral voluntary phase of the swallow may be related to corticobulbar and corticopontine degeneration (a hallmark feature of FRDA) (Pandolfo, 2009). Diminished pharyngeal and laryngeal sensitivity may be a manifestation of sensory peripheral neuropathy (also a sequela of FRDA) (Morral, Davis, Qian, Gelman & Koeppen, 2010) and warrants further investigation. Future research could consider measures of laryngeal sensitivity in the FRDA population (via cough reflex testing, for example), as well as the reliability of other non-instrumental measures of swallowing in predicting aspiration in this population, including pulse oximetry.

6.9.6 Limitations of the present study

The current study has some limitations. Despite being the largest cohort study of swallowing in Friedreich ataxia to date, the relatively small sample size may have impacted our capacity to identify predictors of aspiration. Whilst adequate for characterisation, the sample size of 38 made distribution and division of the data difficult, especially as the sample was dichotomised to identify predictors of aspiration. Due to time constraints, this study may have been under-powered. The lack of significant results (in the identification of predictors of aspiration) is likely due to a Type II error due to the small sample size.

Although this study showed aspiration to be present in a third of individuals with FRDA, the clinical implications of aspiration in this condition remain unclear. Data pertaining to the frequency of aspiration-related pneumonia in the FRDA population is limited. An important next step in this research would be to determine the causal relationship, if any, between aspiration and the presence of pneumonia in FRDA. Another limiting factor is the small number of pediatric participants (<18 years) included in this study (four in total completed the Swal-QOL, two completed the FDA-2, and one participated in VFSS), meaning the spectrum of FRDA disease severity may not be completely captured in this study.

Objectively and accurately measuring swallowing function is not currently possible. Standardised protocols with published data on reliability and validity, such as the Modified Barium Swallowing Impairment profile (MBSImp) (Martin-Harris et al., 2008), require specialised training and associated costs. Whilst the VFSS procedure in this study was controlled, interpretation of VFSS remains relatively subjective in terms of judging the amount and severity of residue in the oral cavity and pharynx. Another limitation is the limited blinding in this study. VFSS and FDA-2 ratings were conducted by the primary author who was not blinded. Therefore, it is acknowledged this study design has the potential for bias. Attempts were made to minimise bias by consecutive recruitment of participants and by following a standard protocol for each participant.

6.10 Summary

This study has demonstrated oral and pharyngeal phase dysphagia is prevalent in FRDA and appears to worsen in line with disease duration and severity. Despite this, no significant relationships were found between aspiration and disease clinical markers, meaning FRDA-affected individuals are at risk of aspiration at any time during disease progression. Critically, individuals with FRDA demonstrate silent aspiration calling into questions the validity of the bedside swallowing assessment in this population. The risk of aspiration in FRDA was not able to be predicted in this cohort, necessitating regular monitoring and evaluation of swallowing function. VFSS remains the only measure to reliably determine airway compromise during swallowing in individuals with FRDA. Auxiliary research is required to better inform the aetiology of FRDA-related dysphagia and determine why silent aspiration occurs in this population.

Chapter 7 Study 4 - A longitudinal analysis of swallowing in individuals with FRDA

7.1 Research questions

The previous chapter described a study (Study 3 - A videofluoroscopic analysis of swallowing in individuals with FRDA) confirming significant correlations between dysphagia and FRDA disease duration and severity, suggesting swallowing impairment is progressive in this population. Study 4 will investigate the progression of dysphagia in FRDA between two time points, approximately 12 months apart (the period of time between two clinical visits to the Friedreich Ataxia Clinic, Melbourne). Data will inform the impact of disease progression on swallowing function, as well as management.

7.2 Aims and hypotheses

Aim 1 - To determine the rate of dysphagia progression in FRDA.

Hypothesis - It is hypothesised swallowing function (as assessed using Swal-QOL, FDA-2 and VFSS) will worsen over the duration of this study.

7.3 Rationale

Dysphagia is commonly experienced by individuals with FRDA and is related to disease duration and severity, suggesting swallowing progressively diminishes in this population. This study will measure the rate of dysphagia progression over one year using scales deemed best clinical practice. An understanding of the relationship between disease and dysphagia progression is important to guide management and intervention (Higo, Tayama, & Nito, 2004; Luchesi, Kitamura, & Mourao, 2015; Strand, Miller, Yorkston, & Hillel, 1996), given dysphagia treatment has been shown to be less effective in the later stages of other neurodegenerative diseases (Higo et al., 2004). Longitudinal data on swallowing function in FRDA will also provide valuable information pertaining to the clinical course of the disease as presently there are no norms predicting rates of change in FRDA-related dysphagia.

7.4 Background

Dysphagia is common in individuals with FRDA, affecting close to 100% of individuals with the disease (Chapter 4). Dysphagia (with concomitant aspiration) can occur at any stage of the disease and can affect the oral and pharyngeal phases of swallowing, reflecting underlying motor and sensory impairments (Chapter 6). Swallowing function related to FRDA is characterised by impaired bolus preparation and transfer, delayed reflex initiation, and impaired pharyngeal clearance (Chapter 6). Further, dysphagia imposes significant

burden on the mental health and quality of life of affected individuals with FRDA (Chapter 4). Dysphagia is related to FRDA severity and duration (Study 3 - A videofluoroscopic analysis of swallowing in individuals with FRDA), however the rate at which swallowing changes over time is unknown.

Measuring and characterising FRDA symptom progression is important for the development of new interventions. Further, investigating the pattern of symptom progression allows for the development of models to predict rate of change in the disease. Age at disease onset, age at time of assessment, length of the GAA1 allele, and whether the individual is having active pharmacological treatment are all associated with progression of FRDA (Delatycki et al., 2009; Friedman et al., 2010; Ribaï et al., 2007). Neurological, physical, cardiological and oculomotor symptoms associated with FRDA are shown to worsen significantly over time (Ribaï et al., 2007). Ribaï and colleagues (2007) evaluated the clinical course of progression in 113 individuals with FRDA annually over a period of seven years. Neurological function, as measured by the ICARS, was shown to significantly deteriorate over one year, with rate of progression significantly correlation with age at onset. In the same cohort, left ventricular mass was seen to decrease, as did posterior wall thickness and septic wall thickness of the heart. The decrease of the posterior wall thickness was greater in patients with GAA expansion length greater than 2000. Visual function was also noted to change, with a slight increase was observed in individuals' square wave jerks. In a subset of the same study, improvements were subjectively reported by the participants in speech function (reported by 14% of participants, n=29/95), fatigue (17%, n=16/95), writing (14%, n=13/95) and gait (12%, n=11/95), whilst worsening of gait and swallowing was reported by 22% (n=21/95) and 11% (n=10/95) participants respectively. Progression was notably slower in individuals seeking active treatment, and in those with onset prior to 15 years (Ribaï et al., 2007).

Oromotor function and speech have been shown to change over time in FRDA (Rosen et al., 2012). Rosen and colleagues assessed the speech of 29 individuals with FRDA across four years at yearly intervals. Acoustic measures were recorded pertaining to pause duration, utterance duration, spectral variation and rhythm spectra. Additional perceptual ratings were made to examine the relationship between acoustic measures and perception of dysarthria. Repeated measures ANOVA revealed significant changes over time (at yearly intervals) in regards to utterance duration (temporal duration of utterances), spectral variation (rate of spectral change and degree of spectral change), and rhythm spectra (peak frequency of the rhythm spectra). These data show that measurable changes occur in speech function within

four years in individuals with FRDA, with subtle changes detected at yearly intervals. This has implications for how clinicians and physicians measure disease progression, as well as therapy outcomes.

Dysphagia has been proven to be progressive in similar conditions to FRDA and frequently mirrors the course of the disease (Daniels, 2006). In ALS, dysphagia progression has been shown to be dependent on the site of disease onset (bulbar or limb onset) (Higo et al., 2004; Shoji et al., 2015) and parallels progression of speech intelligibility (Strand et al., 1996). Furthermore, a progressive decrease in respiratory function has been shown to impact on swallowing function in the ALS population (Shoji et al., 2015). An understanding of the relationship between disease and dysphagia progression is important to guide management and intervention (Higo, Tayama, & Nito, 2004; Luchesi, Kitamura, & Mourao, 2015; Strand, Miller, Yorkston, & Hillel, 1996), given dysphagia treatment has been shown to be less effective in the later stages of other neurodegenerative diseases (Higo et al., 2004). Longitudinal data on swallowing function in FRDA will also provide valuable information pertaining to the clinical course of the disease and further inform understanding of the pathophysiology of FRDA. Presently there are no norms predicting rates of change in FRDA-related dysphagia. This is a critical lack given the need for reliable measures in clinical and therapeutic trials. Knowledge of how FRDA impacts on swallowing over time will inform understanding of the disease. Secondly, findings will elucidate timing, efficacy and type of dysphagia intervention, including the introduction of enteral feeding.

7.5 Methods

7.5.1 Participants

Twenty-three of the original 59 (38.98%) participants participated in the time point 2 (TP2) assessments. Seventeen participants repeated the Swal-QOL ($\bar{x}$ age 37.48 years, σ 13.71 years). Nine of the original 35 participants (25.71%) participated in repeat FDA-2 assessment. Twelve participants (31.58%) went on to have a repeat VFSS.

Repeated assessments were completed as close to 12 months apart as possible so to coincide with the participants' yearly visit to the FRDA clinic. On average, Swal-QOL assessment was conducted 332.4 days apart (range 194 to 423 days), FDA-2 416.1 days (range 306 to 540 days), and VFSS 365 days (range 190 to 456 days).

7.5.2 Assessment

The progression of dysphagia in individuals with FRDA was measured using the protocols outlined in Study 1 - Swallowing-related quality of life in individuals with Friedreich ataxia (Chapter 4), Study 2 – Clinical bedside examination of oromotor function and swallowing in FRDA using a standardised assessment (Chapter 5), and Study 3 - A videofluoroscopic analysis of swallowing in individuals with FRDA (Chapter 6).

7.5.3 Statistical analysis

Characterising swallowing impairment

Descriptive statistics were used to define the observed swallowing deficits, and report frequency of penetration and aspiration as evident on VFSS (interpreted using the PAS and the aspiration domain of the BAS).

Relationships between swallowing impairment and FRDA clinical parameters

Given the non-parametric nature of the data, Spearman's rho (ρ) was used to investigate the relationship between swallowing function and other FRDA clinical parameters (including age at time of disease onset and assessment, disease duration, GAA repeat size on the smaller (GAA1) and larger (GAA2) *FXN* allele, and disease severity [FARS score]).

Mapping the clinical course of FRDA-related dysphagia

Differences in results between the time points (paired results) were calculated via Wilcoxon Signed Rank Tests due to the non-parametric nature of the data. Effect size (r) was calculated by the formula proposed by Pallant (2005) ($r = z/\sqrt{N}$). Values were interpreted according to those proposed by Cohen (Cohen, 1988), whereby 0.1 – 0.3 = small effect, 0.3 – 0.5 = medium effect, and >0.5 = large effect.

Reliability

Interrater and intrarater reliability where determined using Gwet's Agreement Coefficient (Gwet, 2015), with values as stipulated by Viera and Garrett (2005): < 0 - *Less than chance agreement*; 0.01 to 0.20 - *Slight agreement*; 0.21 to 0.40 - *Fair agreement*; 0.41 to 0.60 - *Moderate agreement*; 0.61 to 0.80 - *Substantial agreement*; 0.81 to 0.99 - *Almost perfect agreement* (Viera & Garrett, 2005). Each VFSS was conducted jointly by a qualified Speech Pathologist trained in VFSS administration and interpretation (the author), and a radiographer. A radiologist observed each VFSS to assess for any structural abnormalities within the upper digestive tract. Each VFSS was rated by the author, with repeat ratings

conducted at least three months apart to calculate intrarater reliability. A second rater (an experienced Speech Pathologist with five years of experience in VFSS interpretation) provided ratings to establish interrater reliability. The second rater was blinded to the participant.

Software

Statistical analysis was performed using SPSS Statistical Software Version 22.0 (SPSS®IBM Corporation, Armonk, New York, USA), and AgreeStat (Gwet, 2015).

7.6 Results

7.6.1 Participant characteristics

Refer to Table 7.1for demographic characteristic of the participant groups at TP1 and TP2.

7.6.2 Reliability

Intrarater reliability

Overall intrarater reliability was GAC 0.97 (p=0.000), indicating *almost perfect agreement*. Reliability for individual parameters ranged from GAC 0.50 (p=0.00) for *Residue in Valleculae* (biscuit), indicating *moderate agreement*, to GAC 1.00 (p=0.00) for *Tongue Function* (fluid), *Jaw Function* (fluid), and PAS (fluid), indicating perfect agreement.

Interrater reliability

Overall interrater reliability was GAC 0.90 (p=0.000). Reliability for individual parameters ranged from GAC 0.40 (p=0.20) for *Tongue Function* (fluid) to GAC 1.00 (p=0.00) for *Lip Function* (fluid, puree, biscuit), *Jaw function* (fluid, puree, biscuit), *Soft Palate Elevation* (fluid, puree, biscuit), *Site of swallow reflex* (puree), *Aspiration* (fluid), *Pharyngeal function* (fluid), and *Cricopharyngeal function* (puree and biscuit). The lowest level of agreement was GAC 0.40 (p=0.20) for *Tongue function* (fluid) (Table 7.2).

Table 7-1 Descriptive statistics and assessment performance of participants at TP1 and TP2 (n=23)

ID	GAA1	GAA2	Age at disease onset	Disease duration (at time of VFSS)		FARS		Swal-QOL		FDA-2		VFSS					
				TP1 (n= 38)	TP2 (n= 12)	TP1 (n= 51)	TP2 (n= 22)	TP1 (n= 59)	TP2 (n= 17)	TP1 (n= 35)	TP2 (n= 9)	TP1 (n=38 [fluid and biscuit', 36 [puree])			TP2 (n=12 for all consistencies)		
												F	P	B	F	P	B
FA001	706	811	13	30.28	31.24	106.5	110	88.18		56	81	1	1	1	1	1	1
FA002	1099	1099	5					59.53	66.54	102		1	2	2			
FA005	720	720	14	15.66	16.66	66	74	95.37	95.37	64		1	1	1	2	1	1
FA006	720	720	15			68	73.5	85.37	84.55	70		1	1	1			
FA007	645	771	3			127.5	123	48.97	69.55	115		1	2	1			
FA012	650	900	14			129	120.5	83.12	88.07	84		1	1	1			
FA013	447	967	18			102	103.5	72.34	84.51	56		2	2	1			
FA015	642	1132	8	31.37	32.62	136	136.5	54.35	59.16	94	106	2	2	1	7	2	1

FA016	606	986	28	26.05	26.97	102.5	101	82.54	87.80	60	71	1	2	1	2	1	1
FA021	780	980	7	43.71	45.11	138.5	134	60.32		124		8		4	8	4	8
FA029	833	835	14	17.74	18.74	95.5	97	84.28	87.58	84	68	1	8	1	8	8	1
FA032	569	884	14	9.84	10.94	77	95.5	91.83	75.68	54	76	1	2	1	7	2	1
FA034	462	462	21			84.5		20.93	14.41	62		8	1	1			
FA037	800	800	3	18.5	19.39	109.5	111	81.82		76	86	2	2	1	2	4	1
FA039	733	943	8	25.97	26.66	117.5		100.00	96.92	74		1	1	1	8	1	1
FA041	593	957	10			48.5		95.62									
FA046	489	1207	18	46.31	46.83	140	143	80.56	76.77			8	4	4	8	4	8
FA047	589	589	17					68.07		98	118	8	4	4			
FA048	853	853	14	27.04	27.96			78.64	69.38	86	88	4	1	1	7	1	1
FA050	998	998	7			96.5	99	68.73	69.71			1	1	1			
FA051	556	733	4			66	76	85.71	100.00								
FA052	690	690	16			109.67	113.5	79.70	80.87	70							
FA054	674	803	32	16.58	17.96	84	86	77.81		56	53	4	8	4	2	2	1

Mean	627.53	863.73	15.37	21.76	26.75	91.14	99.68	75.82	77.82	72.66	78.00	3.03	2.00	1.47	5.17	2.58	2.17
σ	193.14	196.97	7.69	10.28	11.05	36.46	23.01	17.88	19.81	26.20	23.22	2.76	1.76	1.37	3.01	2.11	2.72
Range	126-1099	320-1345	3-34	4.74-46.31	10.94-46.31	37.50-140	56-143	48.97-100	14.41-100	34-126	39-118	1-8	1-8	1-8	1-8	1-8	1-8

TP1 – Time point 1, TP2 – Time point 2, F – fluid, P – Puree, B – Biscuit. Swal-QOL: Swallowing Quality of Life Questionnaire; FDA-2: Frenchay Dysarthria Assessment (2nd edition); PAS: Penetration-Aspiration Scale. The optimal score on the Swal-QOL of 220 indicates normal swallowing with any deviation from this score indicating a degree of impairment. The FDA-2 consists of 26 items and each is scored on a scale from 1 (normal function) to 9 (no function). Therefore FDA-2 scores range from 26 to 234, and scores increase with severity.

Table 7-2 Reliability of VFSS results at TP1 and TP2

				Intra rater reliability		Interrater reliability	
				GAC	p-value	GAC	p-value
Bethlehem Assessment Scale	Oral phase	Lip function	Fluid	0.91	0.00*	1.00	n/a
			Puree	0.63	0.02*	1.00	n/a
			Biscuit	0.80	0.00*	1.00	n/a
		Tongue function	Fluid	1.00	0.00*	0.40	0.20
			Puree	0.86	0.00*	0.91	0.00*
			Biscuit	0.75	0.00*	0.89	0.00*
		Jaw function	Fluid	1.00	0.00*	1.00	n/a
			Puree	0.91	0.00*	1.00	n/a
			Biscuit	0.91	0.00*	1.00	n/a
	Pharyngeal phase	Soft palate elevation	Fluid	0.73	0.00*	1.00	n/a
			Puree	0.92	0.00*	1.00	n/a
			Biscuit	0.86	0.00*	1.00	n/a
		Site of swallow reflex initiation	Fluid	0.89	0.00*	0.93	0.00*
			Puree	0.94	0.00*	1.00	n/a
			Biscuit	0.94	0.00*	0.97	0.00*
		Aspiration	Fluid	0.94	0.00*	1.00	n/a
			Puree	0.89	0.00*	0.97	0.00*
			Biscuit	0.97	0.00*	0.89	0.00*
		Residue in the valleculae	Fluid	0.50	0.00*	0.50	0.08
			Puree	0.85	0.00*	0.88	0.00*
			Biscuit	0.96	0.00*	0.96	0.00*

	Residue in the pyriform sinuses	Fluid	0.74	0.00*	0.95	0.00*
		Puree	0.87	0.00*	0.94	0.00*
		Biscuit	0.76	0.00*	0.94	0.00*
	Pharyngeal function	Fluid	0.90	0.00*	1.00	n/a
		Puree	0.74	0.00*	0.93	0.00*
		Biscuit	0.92	0.00*	0.92	0.00*
	Cricopharyngeal function	Fluid	0.88	0.00*	0.89	0.00*
		Puree	0.94	0.00*	1.00	n/a
		Biscuit	0.65	0.00*	1.00	n/a
Penetration-Aspiration Scale		Fluid	1.00	0.00*	0.97	0.00*
		Puree	0.84	0.00*	1.00	n/a
		Biscuit	0.63	0.00*	1.00	n/a
Overall agreement			0.84	0.00*	0.58	0.00*

*significant at $p<0.05$

7.6.3 Swal-QOL

Overall Swal-QOL scores did not significantly differ between the time points (TP1 x̄ 74.82, *σ* 19.58, TP2 x̄ 76.82 *σ 19.81,* Z=-0.98, p=0.33, r=0.24), however significant changes in impairment was seen for items related to Symptom frequency (TP1 x̄ 74.05, σ 18.77, TP2 x̄ 69.12, σ *22.22,* Z=-2.18, p=0.03, r=-0.52) and Sleep (TP1 x̄ 59.56, σ 32.23; TP2 x̄ 75.00 σ *26.52,* Z=-2.06, p=0.04, r=0.35). A significant improvement was noted in the Food Selection domain (TP1 x̄ 80.88, σ 23.43, TP2 x̄ 88.97 σ 21.41, Z=-2.21, p=0.03, r=-0.54).

Analysis of the 44 individual Swal-QOL items revealed significant progression in two items from TP1 to TP2, Food Selection - Figuring out what I can and can't eat is a problem for me (TP1 x̄ 4.00, σ 1.22, TP2 x̄ 4.53 σ *0.87,* Z=-2.26, p<0.05, r=0.39), and Sleep – Have trouble staying asleep? (TP1 x̄ 3.24, σ 1.39, TP2 x̄ 4.24 σ *1.15,* Z=-2.06, p<0.05, r=0.35). An improvement was observed in one sub item - Communication - It's been difficult for me to speak clearly (TP1 x̄ 4.18 σ 0.81, TP2 x̄ 3.71 σ 0.85, p<0.05, r=0.34) (Table 7.4).

7.6.4 Oromotor function

Overall FDA-2 scores did not significantly differ between TP1 and TP2 (TP1 x̄ 76.00, *σ* 21.77, TP2 x̄ 78.60 *σ 23.33,* Z=-1.40, p=0.31, r=033). Significant reduction in function was observed in Respiration only (TP1 x̄ 2.83, σ 0.79, TP2 x̄ 3.15 σ 0.65, *Z*=-2.83, p=0.01, r=0.67) (Table 7.5). Only one sub-item on the FDA-2 was statistically different at the second time point (Lips – Seal TP1 x̄ 2.67, σ 1.22, TP2 x̄ 3.30 σ 1.16, Z=-2.07, p=0.04, r=0.49) (Table 7.5).

7.6.5 VFSS

Comparisons between the 12 participants who completed assessment at TP1 and TP2 revealed significant progression in Tongue function (biscuit) (TP1 x̄ 2.75, σ 0.75, TP2 x̄ 3.08, σ 0.67, Z=-2.121, p=0.03, r=0.43), Residue in Valleculae (puree) (TP1 x̄ 2.36, σ 0.92, TP2 x̄ 2.67, σ 0.72, Z=-2.000, p=0.05, r=0.41), Pharyngeal function (puree) (TP1 x̄ 2.42, σ 0.91, TP2 x̄ 2.50, σ 0.80, Z=-2.646, p=0.01, r=0.54), and Cricopharyngeal function (biscuit) (TP1 x̄ 2.25, σ 1.06, TP2 x̄ 2.67, σ 0.98, Z=-2.33, p=0.02, r=0.48) (Table 7.7). Individual participant's results out outlined in Table 7.10, Table 7.11, and Table 7.12.

Penetration and aspiration

Three participants (25%) demonstrated aspiration (PAS ≥ 6) on at least one consistency at TP2, and 2/12 (41.67%) demonstrated penetration (PAS ≥ 2). Aspiration occurred most

frequency with fluid (2/12, 16.67% of participants). No significant differences were observed for penetration and aspiration at TP2 compared to TP1 (Table 7.7).

Table 7-3 Comparison of Swal-QOL item scores at TP1 and TP2 (n=17)

Swal-QOL items		TP1				TP2				Wilcoxon signed ranks test	Effect size (r)
		Min	Max	$\bar{x}$	σ	Min	Max	$\bar{x}$	σ		
Burden	Dealing with my swallowing problem is very difficult	2	5	4.35	1.06	2	5	4.18	1.01	Z=-1.13, p=0.26	r=0.19
	My swallowing problem is a major distraction in my life	2	5	4.41	1.06	2	5	4.41	1.00	Z=0.00, p=1.00	r=0.00
Eating Desire	Most days, I don't care if I eat or not	1	5	4.47	1.18	1	5	4.59	1.00	Z=-0.45, p=0.66	r=0.08
	I'm rarely hungry anymore	1	5	4.06	1.48	1	5	4.29	1.21	Z=-0.65, p=0.52	r=0.11
	I don't enjoy eating anymore	1	5	4.53	0.87	2	5	4.59	0.87	Z=-0.33, p=0.74	r=0.06
Eating Duration	It takes me longer to eat than other people	1	5	3.18	1.42	1	5	2.82	1.63	Z=-1.30, p=0.19	r=0.22
	It takes me forever to eat a meal	2	5	4.06	1.25	1	5	3.53	1.37	Z=-1.90, p=0.06	r=0.33

Symptom Frequency	Coughing	1	5	3.24	0.97	1	5	3.00	1.06	Z=-0.59, p=0.56	r=0.10
	Choking when you eat food	2	5	3.71	1.10	1	5	3.47	1.01	Z=-1.27, p=0.21	r=0.22
	Choking when you take liquids	2	5	3.53	1.01	1	5	3.23	1.09	Z=-1.67, p=0.10	r=0.29
	Having thick saliva or phlegm	2	5	4.06	1.03	1	5	3.65	1.50	Z=-1.59, p=0.11	r=0.27
	Gagging	1	5	4.06	1.20	1	5	4.06	1.03	Z=-0.06, p=0.95	r=0.01
	Drooling	2	5	4.06	1.03	2	5	3.88	1.05	Z=-1.13, p=0.26	r=0.19
	Problems chewing	1	5	4.41	0.71	2	5	4.29	0.98	Z=-0.71, p=0.48	r=0.12
	Having excess saliva or phlegm	2	5	4.29	0.99	1	5	3.82	1.42	Z=-1.81, p=0.07	r=0.31
	Having to clear your throat	1	5	3.24	1.03	1	5	3.12	0.99	Z=-0.54, p=0.59	r=0.09
	Food sticking in your throat	1	5	4.12	1.11	1	5	3.71	1.21	Z=-1.93, p=0.05	r=0.33
	Food sticking in the mouth	1	5	4.00	1.17	1	5	4.00	1.17	Z=0.00, p=1.00	r=0.00
	Food or liquid dribbling out of your mouth	3	5	4.29	0.69	2	5	4.12	0.26	Z=-1.00, p=0.32	r=0.17
	Food or liquid coming out of your nose	2	5	4.41	0.87	2	5	4.47	0.94	Z=-0.12, p=0.90	r=0.02
	Coughing food or liquid out of your mouth when it gets stuck	2	5	4.06	0.90	1	5	3.88	1.05	Z=-0.91, p=0.37	r=0.16

Food Selection	Figuring out what I can and can't eat is a problem for me	2	5	4.00	1.22	2	5	4.53	0.87	Z=-2.26, p=0.02*	r=0.39
	It is difficult to find foods that I both like and can eat	2	5	4.47	0.87	2	5	4.59	0.87	Z=-1.00, p=0.32	r=0.17
Communication	People have a hard time understanding me	2	5	4.00	0.94	2	5	3.71	0.92	Z=1.12, p=0.27	r=0.19
	It's been difficult for me to speak clearly	2	5	4.18	0.81	2	5	3.71	0.85	Z=-2.00, p=0.05*	r=0.34
Fear	I fear I may start choking when I eat food	1	5	3.82	1.19	1	5	4.06	1.14	Z=-1.27, p=0.21	r=0.22
	I worry about getting pneumonia	2	5	4.53	0.87	2	5	4.76	0.75	Z=-1.63, p=0.10	r=0.28
	I am afraid of choking when I drink liquids	1	5	3.76	1.09	1	5	3.71	1.21	Z=-0.38, p=0.71	r=0.07
	I never know when I am going to choke	1	5	3.47	1.37	1	5	3.65	1.22	Z=-0.28, p=0.78	r=0.05

Mental Health	My swallowing problem depresses me	3	5	4.76	0.56	2	5	4.76	0.75	Z=0.00, p=1.00	r=0.00
	Having to be so careful when I eat or drink annoys me	1	5	4.00	1.17	2	5	4.12	0.93	Z=-0.71, p=0.48	r=0.12
	I've been discouraged by my swallowing problem	2	5	4.35	0.93	2	5	4.47	0.80	Z=-1.00, p=0.32	r=0.17
	My swallowing problem frustrates me	1	5	4.06	1.25	1	5	4.18	1.24	Z=-0.71, p=0.48	r=0.12
	I get impatient dealing with my swallowing problem	1	5	4.24	1.25	1	5	4.47	1.07	Z=-0.71, p=0.48	r=0.12
Social	I do not go out because of my swallowing problem	2	5	4.35	1.22	1	5	4.71	0.99	Z=-1.30, p=0.19	r=0.22
	My swallowing problem makes it hard to have a social life	2	5	4.53	1.07	2	5	4.76	0.75	Z=-1.34, p=0.18	r=0.23
	My usual work or leisure activities have changed because of my swallowing problem	2	5	4.53	0.94	2	5	4.71	0.77	Z=-1.13, p=0.26	r=0.19

	Social gatherings (like holidays or get-togethers) are not enjoyable because of my swallowing problem	2	5	4.65	0.70	2	5	4.71	0.77	Z=-0.45, p=0.66	r=0.08
	My role with family and friends gas changed because of my swallowing problem	2	5	4.76	0.56	2	5	0.71	0.77	Z=-0.58, p=0.47	r=0.10
Fatigue	Feel weak?	1	5	3.47	1.37	1	5	3.76	0.28	Z=-0.73, p=0.47	r=0.13
	Feel tired?	1	5	2.94	1.20	1	5	3.52	1.33	Z=-1.72, p=0.09	r=0.29
	Feel exhausted?	1	5	3.06	1.25	1	5	3.65	1.32	Z=-1.91, p=0.06	r=0.33
Sleep	Have trouble falling asleep?	1	5	3.53	1.42	1	5	4.24	1.15	Z=-2.05, p=0.04*	r=0.35
	Have trouble staying asleep?	1	5	3.24	1.39	1	5	3.76	1.20	Z=-1.85, p=0.06	r=0.32

*significant at $p<0.05$

Table 7-4 Comparison of Swal-QOL domain scores at TP1 and TP2 (n=17)

Swal-QOL domains	TP1				TP2				Wilcoxon signed ranks test	Effect size (r)
	Min	Max	$\bar{x}$	σ	Min	Max	$\bar{x}$	σ		
Burden	25	100	84.56	26.34	25	100	82.35	24.63	Z=-0.43, p=0.67	r=-0.10
Eating desire	17	100	83.82	23.10	8	100	87.25	23.78	Z=-0.85, p=0.40	r=0.15
Eating duration	0	100	65.44	30.47	0	100	54.41	36.16	Z=-1.85, p=0.07	r=-0.44
Symptom frequency	29	100	74.05	18.77	9	100	69.12	22.22	Z=-2.18, p=0.03*	r=-0.52
Food selection	38	100	80.88	23.43	25	100	88.97	21.14	Z=-2.21, p=0.03*	r=-0.54
Communication	50	100	77.21	20.37	25	100	67.65	21.68	Z=-1.60, p=0.11	r=0.27
Fear	13	100	72.43	25.01	6	100	76.10	23.72	Z=-0.92, p=0.36	r=0.16
Mental health	45	100	82.06	23.92	15	100	85.00	22.36	Z=-1.00, p=0.31	r=0.17
Social	40	100	89.12	19.54	20	100	92.94	20.00	Z=-1.08, p=0.28	r=0.19
Fatigue	0	100	53.92	30.49	0	100	66.18	29.82	Z=-1.34, p=0.180	r=0.23
Sleep	0	100	59.56	33.23	0	100	75.00	26.52	Z=-2.06, p=0.04*	r=0.35
Total	21	100	74.82	19.58	14.41	100	76.82	19.81	Z=-0.98, p=0.33	r=0.24

*significant at $p<0.05$

Table 7-5 Comparison of FDA-2 at TP1 and TP2 (n=9)

FDA-2 domains and sub-items		TP1				TP2				Wilcoxon signed ranks test	Effect size (r)
		Min	Max	$\bar{x}$	σ	Min	Max	$\bar{x}$	σ		
Reflexes	Cough	1.00	5.00	3.22	1.20	1.00	5.00	3.40	1.26	Z=-0.82, p=0.41	r=0.19
	Swallow	1.00	5.00	3.22	1.20	1.00	5.00	3.50	1.58	Z=-1.13, p=0.26	r=0.27
	Dribble/Drool	1.00	5.00	1.89	1.45	1.00	5.00	2.50	1.58	Z=-1.23, p=0.22	r=0.29
Respiration	Rest	1.00	5.00	2.89	1.05	1.00	5.00	3.30	1.34	Z=-1.06, p=0.29	r=0.25
	In Speech	1.00	5.00	2.78	1.20	1.00	5.00	3.00	1.33	Z=-1.00, p=0.32	r=0.24
Lips	Rest	1.00	3.00	1.22	0.67	1.00	3.00	1.40	0.84	Z=-0.58, p=0.56	r=0.14
	Spread	1.00	3.00	1.22	0.67	1.00	1.00	1.00	0.00	Z=-1.00, p=0.32	r=0.24
	Seal	1.00	5.00	2.67	1.22	1.00	5.00	3.30	1.16	Z=-2.07, p=0.04*	r=0.49
	Alternate	1.00	5.00	3.22	0.67	3.00	5.00	3.30	0.67	Z=-0.45, p=0.66	r=0.11
	In Speech	3.00	5.00	3.44	0.88	3.00	5.00	3.40	0.70	Z=-0.14, p=0.89	r=0.03
Palate	Fluids	1.00	3.00	1.22	0.67	1.00	3.00	1.30	0.67	Z=-1.00, p=0.32	r=0.24
	Maintenance	1.00	3.00	1.44	0.88	1.00	5.00	1.70	1.34	Z=-1.34, p=0.18	r=0.32
	Speech	3.00	5.00	3.67	1.00	1.00	7.00	4.10	1.66	Z=-1.89, p=0.06	r=0.45

Laryngeal	Time	1.00	5.00	3.00	1.73	1.00	7.00	3.40	2.27	Z=-0.83, p=0.41	r=0.20
	Pitch	3.00	9.00	5.22	2.11	1.00	7.00	4.60	1.90	Z=-0.41, p=0.68	r=0.10
	Volume	3.00	7.00	4.78	1.56	3.00	7.00	5.50	1.43	Z=-1.72, p=0.09	r=0.41
	In speech	3.00	5.00	3.67	1.00	1.00	7.00	3.80	1.62	Z=-0.97, p=0.33	r=0.23
Tongue	Rest	1.00	3.00	2.11	1.05	1.00	3.00	1.70	0.95	Z=-0.56, p=0.58	r=0.13
	Protrusion	1.00	5.00	2.56	1.67	1.00	5.00	3.00	1.33	Z=-0.63, p=0.53	r=0.15
	Elevation	1.00	5.00	3.44	1.33	3.00	7.00	3.60	1.35	Z=-0.58, p=0.56	r=0.14
	Lateral	1.00	3.00	2.11	1.05	1.00	5.00	2.30	1.34	Z=-0.72, p=0.47	r=0.17
	Alternate	3.00	5.00	4.11	1.05	3.00	5.00	3.60	0.97	Z=-1.41, p=0.16	r=0.33
	Speech	3.00	5.00	4.11	1.05	1.00	5.00	3.90	1.45	Z=-0.58, p=0.56	r=0.14
Intelligibility	Words	1.00	3.00	1.89	1.05	1.00	5.00	2.80	1.14	Z=-1.89, p=0.06	r=0.45
	Sentences	1.00	5.00	2.33	1.41	1.00	3.00	2.60	0.84	Z=-1.00, p=0.32	r=0.24
	Conversation	1.00	3.00	2.33	1.00	1.00	3.00	2.60	0.84	Z=-1.00, p=0.32	r=0.24
Total FDA2 score		54.00	118.00	76.00	21.77	39.00	118.00	78.60	23.22	Z=-1.40, p=0.31	r=0.33

*significant at $p<0.05$

Table 7-6 FDA-2 domains at TP1 and TP2 (n=9)

FDA-2 domains	TP1		TP2		Wilcoxon signed ranks test	Effect size (r)
	Arithmetic $\bar{x}$	σ	Arithmetic $\bar{x}$	σ		
Reflexes	2.78	0.88	3.13	0.99	Z=-1.02, p=-0.31	r=0.24
Respiration	2.83	0.79	3.15	0.64	Z=-2.83, p=0.01*	r=0.67
Lips	2.36	0.37	2.48	1.28	Z=-0.56, p=0.58	r=0.13
Palate	2.11	0.75	2.37	1.70	Z=-1.89, p=0.06	r=0.45
Laryngeal	4.17	1.35	4.33	1.38	Z=-1.26, p=0.21	r=0.30
Tongue	3.07	0.80	3.02	1.16	Z=-0.14, p=0.89	r=0.03
Intelligibility	2.19	1.04	2.67	0.12	Z=-1.79, p=0.07	r=0.42

*significant at $p<0.05$

Table 7-7 Comparison of VFSS at TP1 and TP2 (n=12)

BAS parameters		TP1				TP2				Wilcoxon signed ranks test	Effect size (r)
		Min	Max	$\bar{x}$	σ	Min	Max	$\bar{x}$	σ		
Lip function	Fluid	1	2	1.17	0.39	1	2	1.08	0.29	Z=-1.00, p=0.32	r=0.20
	Puree	1	3	1.27	0.47	1	2	1.33	0.49	Z=-1.73, p=0.08	r=0.35
	Biscuit	1	3	1.33	0.49	1	2	1.17	0.52	Z=-1.41, p=0.16	r=0.29
Tongue function	Fluid	1	3	1.50	0.67	1	2	1.42	0.49	Z=0.00, p=1.00	r=0.00
	Puree	1	3	1.91	0.83	2	4	2.33	0.65	Z=-1.41, p=0.16	r=0.29
	Biscuit	1	3	2.75	0.75	2	4	3.08	0.67	Z=-2.12, p=0.03*	r=0.43
Jaw function	Fluid	1	2	1.08	0.29	1	1	1.00	0.00	Z=0.00, p=1.00	r=0.00
	Puree	1	1	1.00	0.00	1	2	1.08	0.29	Z=-1.00, p=0.32	r=0.20
	Biscuit	1	2	1.08	0.29	1	2	1.08	0.29	Z=-1.00, p=0.32	r=0.20
Soft palate function	Fluid	1	4	1.75	0.97	1	2	1.33	0.83	Z=-0.41, p=0.16	r=0.29
	Puree	1	4	1.82	1.17	1	3	1.33	0.83	Z=-0.41, p=0.16	r=0.29
	Biscuit	1	4	1.92	1.16	1	2	1.33	0.83	Z=-1.00, p=0.32	r=0.20

Reflex initiation	Fluid	2	4	2.92	0.67	1	4	2.33	0.65	Z=-1.73, p=0.08	r=0.35
	Puree	2	4	3.00	0.45	1	4	2.25	0.58	Z=-0.41, p=0.16	r=0.08
	Biscuit	2	4	3.08	0.51	1	4	2.50	0.51	Z=-0.41, p=0.16	r=0.08
Aspiration	Fluid	1	3	1.67	0.78	1	4	1.75	0.89	Z=-0.41, p=0.16	r=0.08
	Puree	1	3	1.82	0.75	1	2	1.25	0.94	Z=-0.58, p=0.56	r=0.12
	Biscuit	1	2	1.25	0.45	1	3	1.17	0.78	Z=-1.00, p=0.32	r=0.20
Residue in valleculae	Fluid	1	3	1.50	0.80	1	2	1.58	0.65	Z=-0.58, p=0.56	r=0.12
	Puree	1	4	2.36	0.92	1	4	2.67	0.72	Z=-2.00, p=0.05*	r=0.41
	Biscuit	1	4	3.00	0.95	1	4	2.83	0.79	Z=-1.00, p=0.32	r=0.20
Residue in pyriform sinuses	Fluid	1	3	1.25	0.62	1	3	1.42	0.67	Z=0.00, p=1.00	r=0.00
	Puree	1	3	1.91	0.83	1	3	1.83	0.51	Z=-0.41, p=0.16	r=0.08
	Biscuit	1	3	1.83	0.72	1	4	1.92	0.75	Z=-0.71, p=0.48	r=0.14
Pharyngeal function	Fluid	1	3	1.25	0.62	1	3	1.42	0.67	Z=0.00, p=1.00	r=0.00
	Puree	1	3	2.00	0.89	1	4	2.50	0.80	Z=-2.65, p=0.01*	r=0.54
	Biscuit	1	3	2.17	0.83	1	4	2.33	0.89	Z=-0.41, p=0.16	r=0.08

Cricopharyngeal function	Fluid	1	3	1.33	0.65	1	2	1.25	0.67	Z=-1.00, p=0.32	r=0.20
	Puree	1	3	2.09	0.94	1	4	1.67	0.79	Z=-0.41, p=0.16	r=0.08
	Biscuit	1	4	2.25	1.06	1	4	2.67	0.98	Z=-2.33, p=0.02*	r=0.48
PAS score	Fluid	1	8	2.83	2.66	1	8	2.25	2.49	Z=-0.00, p=1.00	r=0.00
	Puree	1	8	2.91	2.66	1	8	1.67	2.01	Z=-1.00, p=0.32	r=0.20
	Biscuit	1	8	2.08	2.19	1	2	1.17	0.39	Z=-1.00, p=0.32	r=0.20

*significant at <0.05

7.7 Discussion

The data reported in this study informs progression of FRDA-related dysphagia and reveal measurable changes in swallowing function over a one year period in this population. Changes were observed in swallowing-related QOL relating to subjective reporting of symptom frequency, and sleep. Statistically significant oromotor changes were observed in respiration. Dysphagia severity was shown to increase (as observed on VFSS), particularly in relation to pharyngeal clearance of solid textures of food, despite relative maintenance of oromotor function and swallowing-related QOL. These results suggest VFSS is an appropriate measure of disease progression, and is more sensitive than non-instrumental measures of swallowing. The fluctuating nature and general progression of FRDA, level of participants' dysphagia-awareness at the second time point, and limitations of the assessment tools are likely to have impacted on the results of this study.

7.7.1 Progression of dysphagia-related QOL

Overall swallowing-related QOL (as measured by the total Swal-QOL score) did not change over the course of this study, however participants reported experiencing symptoms of dysphagia more frequently on the second assessment. Participants with FRDA also reported significantly increased difficulty selecting appropriate foods to cater for their swallowing difficulties at the second time point. In comparison, difficulty sleeping was less pronounced at the second time point. The limited change in swallowing-related QOL factors was observed despite physiological changes observed in swallowing in VFSS, meaning perceived symptoms to not correlate with underling pathology. The sporadic pattern of swallowing-related QOL in FRDA over time may be influenced by participant awareness and perception of dysphagia. After the primary assessment (TP1), all participants in this study were provided with education regarding normal swallowing, dysphagia, aspiration, and clinical implications of aspiration. Therefore, participants had a level of understanding of swallowing physiology and dysfunction at the time of the second assessment. Symptom perception is reported to influence many facets of health intervention, including health maintenance, accuracy of symptom reporting, and adherence to medical regimes (Phillips, Cornell, Raczynski, & Gilliland, 1999). Dysphagia is known to affect the mental state of those afflicted (Bretan et al., 1995; Ekberg et al., 2002) and it is therefore likely the education participants received in this study influenced their symptom perception. This phenomenon has been previously reported in the literature, with an explanation of the normal swallowing mechanism shown to

improve dysphagia-related depression and anxiety in a sample of five individuals with MS (Bretan et al., 1995).

7.7.2 Progression of FRDA-related oromotor function and dysphagia

Oromotor function (as measured by FDA-2) was grossly preserved with exception of respiratory function over the 12 month period of this study, however dysphagia was shown to progress in the time between analyses, particularly relating to clearance of solid textures of food from the pharynx. Tongue function was also noted to decline. Airway entry (penetration and aspiration) was not significantly different between the groups at TP1 and TP2 however three of the participants demonstrated reflexive airway protective mechanisms at the second time point (all with fluid), which was not observed on initial assessment. Four of the 12 participants (33.33%) presented new signs of significant airway penetration and/or aspiration (determined at PAS ≥ 3) at TP2, and all with fluid. No change in significant airway entry was noted with puree or biscuit. These results suggest that progression of FRDA-related dysphagia can be detected in a 12 month period. These results provide evidence for the need for close monitoring of swallowing as the disease progresses, as individuals with FRDA may require diet and fluid modification to maintain adequate nutrition and hydration.

An interesting observation in this study was the presence of airway protective behaviours at TP2 and not at TP1 (where all those who aspirated did so silently). Three participants (25%) had a PAS score of 7 (Material enters the airway, passes below the vocal folds, and is not ejected from the trachea despite effort) at TP2. Only one of these three participants had demonstrated PAS ≥ 3 on the initial VFSS (score of 4; Material enters the airway, contacts the vocal folds, and is ejected from the airway), suggesting airway protective responses may be diminished in FRDA rather than absent. Further investigation of laryngeal sensitivity in individuals with FRDA is still warranted given the existence of silent aspiration in the population. Other factors may have contributed. Silent aspiration is reported to be volume dependent, meaning a larger volume of aspirated material may result in a reflexive cough in individuals who had previously silently aspirated on smaller amounts (determined in a prospective study of 4102 individuals with heterogeneous dysphagia) (Leder et al., 2011). In the present study it is possible participants aspirated a greater amount of barium at TP2, and thus a cough was initiated (but not effective in ejecting material from the airway). This notion also supports participant subjective reports of coughing with oral intake on Swal-QOL assessment.

7.7.3 Limitations of the present study

Any study of FRDA must account for the fluctuating and variable nature of this disease (Pandolfo, 2002). The slow nature FRDA disease progression (Delatycki & Corben, 2012) suggests that the length of the current study may not have been sufficient to capture significant progression on swallowing function. In a study of dysarthria related to FRDA, significant change in speech function was noted across a two year duration (Rosen et al., 2012). Thus, further analysis of swallowing function in individuals with FRDA over time is warranted, and likely to reveal further change. A larger number of participants would have allowed for better exploration of FRDA-related dysphagia over time, as the small sample size likely underpowered this study and this may have diminished the effect sizes calculated for this study. Further, this study considered FRDA broadly with no controlling for age, gender, disease severity or phenotype. These variables have been previously reported as strongly associated with symptom progression in FRDA (Friedman et al., 2010).

Another consideration is the swallowing assessment tools' responsiveness to change which is likely limited given the poor sensitivity of some measures. Other assessment tools used in FRDA have been shown to have limited responsiveness to change, such as the FAIS (Tai et al., 2015). This longitudinal study must be interpreted taking careful consideration of VFSS, which only provides a snapshot of swallowing ability and is not a true reflection of swallowing function over a whole meal. Furthermore, there was no controlling for fatigue in this study which is may have impacted on participant presentation and performance on VFSS and FDA-2 assessment. Objectively measuring swallowing function is difficult. Whilst the VFSS procedure in this study was controlled, interpretation of VFSS remains relatively subjective in terms of judging the amount and severity of residue in the oral cavity and pharynx, and degree of penetration and/or aspiration.

Participant selection was also problematic. Here, FRDA was considered broadly and no effort was made to separate those with typical FRDA and atypical FRDA, including late onset FRDA which is typically associated with less severe symptoms. Further research should look at differences between these groups. Given the logistics associated with participating in this study (completing a questionnaire, a 20 minute filmed assessment of oromotor function, and a VFSS which at times took up to an hour given the waiting time) it is possible those with less severe symptoms were more willing to participant in repeat assessment, and thus may have biased the sample.

7.7.4 Clinical implications and future directions

Dysphagia is progressive in FRDA with significant progression observed in a period of 12 months. Regular monitoring of dysphagia is an important aspect of disease management, and further research is needed to evaluate whether early intervention would modify the swallowing progression seen in individuals with FRDA. This study provides important methodical knowledge to future trials in FRDA. Significant changes in swallowing function were detected on VFSS, and therefore this may be an appropriate assessment and measure of disease progression to be used in conjunction with disease scales (SARA, FARS and ICARS) over time. However, the limitations of VFSS including necessity for exposure to radiation, time consumption, expense, and the subjectivity of VFSS interpretation, may limit the use of the tool for measuring disease progression.

7.8 Summary

Dysphagia related to FRDA progresses over one year, however symptoms appear to evolve in a non-linear fashion. Dysphagia progression does not correlate with swallowing perception, however dysphagia education is likely to have influenced this disparity. These data provide valuable information and contributes to our understanding of the clinical course of FRDA, and suggest swallowing function is a measurable symptom of the disease. Further investigation of the motor and sensory issues contributing to the dysphagia characteristics observed in FRDA is warranted. The data suggest VFSS is able to detect significant changes in function between yearly clinical appointments.

Chapter 8 Summary, limitations and future directions

8.1 Summary of research and resulting thesis

The purpose of this research was to systematically characterise FRDA-related swallowing function (including site-specific impairment and presence of airway penetration and/or aspiration) using the current clinical standard of swallowing assessment. The data revealed that oral and pharyngeal phase dysphagia is prevalent in FRDA and worsens with disease duration and severity. Significant deterioration in swallowing function can be seen in as little as 12 months in the FRDA population. Aspiration is not predictable in this population and appears to occur at any stage of disease, necessitating the need for regular monitoring and evaluation of swallowing function. VFSS remains the only method to reliably determine airway compromise during swallowing in individuals with FRDA however methods to evaluate function remain subjective. Dysphagia significantly impacts QOL in individuals with FRDA, and management should reflect and address the significant burden associated with swallowing impairment in these individuals.

This research and resulting thesis elucidates our understanding of FRDA and the clinical course of FRDA-related swallowing impairment. The assessments used in this study were carefully selected in line with best clinical practice and describe the nature, severity and impact of dysphagia in FRDA. Predictors of airway compromise during the swallowing process were explored using clinical and behavioural data including psychosocial and oromotor dysfunction. This research provides important information that can be readily adopted into clinical practice, and is an imperative step in defining evidence based treatment approach to this population group.

The first three cross-sectional studies (Study 1 - Swallowing-related quality of life in individuals with Friedreich ataxia, Study 2 – Clinical bedside examination of oromotor function and swallowing in FRDA using a standardised assessment, and Study 3 - A videofluoroscopic analysis of swallowing in individuals with FRDA) described in detail the impact and nature of dysphagia on individuals with FRDA, and characterised the oral and pharyngeal phase deficits experienced by these individuals. Including a sample of healthy adults as a control group in the primary study (investigating impact of dysphagia on QOL) allowed comment on dysphagia patterns in individuals with FRDA compared to those without the disease. From these investigations, it was determined that oral and pharyngeal phase dysphagia is prevalent in FRDA and appears to worsen with disease duration and

severity. Aspiration into the airway, including silent aspiration (whereby no reflexive airway protective mechanism is exhibited in response to airway entry of material during swallowing) is also a characteristic of the disease. Furthermore, aspiration cannot be predicted in this population and appears to occur at any stage of disease, necessitating the need for regular monitoring and evaluation of swallowing function. Pertinently, results of the research show that dysphagia significantly impacts QOL in individuals with FRDA, and management should reflect and address the significant burden associated with swallowing impairment in these individuals. The last study included in this thesis, Study 4 – A longitudinal analysis of swallowing in individuals with FRDA (Chapter 7), is a longitudinal analysis of a subset of participants conducted to map the clinical course of FRDA-related dysphagia. Dysphagia was shown to progress in a non-linear fashion, likely representative of the heterogeneous nature of progression and presentation of the disease. This study provides important methodical knowledge to future therapeutic and clinical trials in FRDA. VFSS was able to detect significant changes in swallowing function over the course of a year which were not detected on non-instrumental measures of swallowing assessment. However, the limitations of VFSS including necessity for exposure to radiation, time consumption, expense, and the subjectivity of VFSS interpretation, may limit the use of the tool for measuring disease progression.

8.2 Limitations of this research

A representative, disease specific sample was recruited for this study and these individuals were assessed using the current clinical standard of assessment, including instrumental analysis. Furthermore, correlations were made with FRDA disease markers allowing these findings to be generalised to the FRDA population despite level of disease severity.

Despite these study strengths, there were a number of potential limitations which may influence analysis and interpretation of data.

i. The most apposite limitation of this study is the sample size (n=59 for whom behavioural data was collected, inclusive of 38 participants who underwent VFSS). Despite being the largest study of FRDA-related dysphagia, larger numbers of participants would have allowed for better exploration of FRDA-related dysphagia and predictors of significant airway entry during swallowing in this population. The small sample size made distribution and division of the data difficult, especially as the sample was dichotomised to identify predictors of aspiration. The non-significant result (in the identification of predictors of aspiration) is possibly due to a Type II error due to the small sample size. It

would be interesting to see if increasing the sample size would in turn increase the power of the statistical analysis.

ii. The slow nature of FRDA disease progression suggests that the length of the current study (12 months) was not long enough to capture any significant impact of disease progression on swallowing function.

iii. Participant selection, whilst adequate for characterisation of swallowing function in the population, may have influenced the data collected. Here, FRDA was considered broadly and no effort was made to separate those with typical FRDA and atypical FRDA, including late onset FRDA which is typically associated with less severe symptoms. This is an important area of further analysis.

iv. Another significant limitation of this body of research is the assessments tools used. Results of *Study 4 – A longitudinal analysis of swallowing in individuals with FRDA* revealed incongruous Swal-QOL results, suggesting that education provided to participants after their initial assessment may have influenced results at the second time point. Almost all participants viewed their VFSS after initial assessment and consequently had a good understanding of swallowing and increased insight and awareness into swallowing function at the second time point assessment. It is possible this knowledge and awareness of dysphagia lessened dysphagia-related anxiety, which may have influenced the results seen in this study. A number of participants reported experiencing dysphagia symptoms more frequently at TP2 with less associated implications on OQL. Despite being in line with best clinical practice, the FDA-2 and VFSS both rely on subjective interpretation which can also be problematic. VFSS can only be considered a 'snapshot' of swallowing ability and not a measure of an individual's true performance over an entire meal. Additionally, the presence of barium can reduce the desirability of food and drink and this can be unpleasant for some patients (Cichero et al., 2000).

v. Factors related to the participant undertaking VFSS also imposes significant variables likely to affect performance on VFSS. These factors may be related to age, fatigue levels, limitations maintaining erect posture, and the presence of any respiratory complications on the day of assessment. In the case of FRDA, postural difficulties (scoliosis) and associated respiratory compromise may impact on coordination between breathing and swallowing, which has been a reported phenomenon in the Cerebral Palsy population (Holmes et al., 2003). Incoordination between breathing and swallowing is known to increase aspiration risk (Martin-Harris, 2006). Further, two participants were unable to participate in VFSS as the equipment could not facilitate the width of their wheelchairs,

and a hoist was not available to transfer these participants to a specialised supportive chair.

8.3 Clinical implications of this research

This research improves our understanding of dysphagia in FRDA and elucidates FRDA progression and clinical presentation. Significant oral and pharyngeal phase swallowing impairment was observed in FRDA, as well as the presence of silent aspiration. Further, dysphagia can progress and manifest in significant airway compromise during swallowing in as little as over a 12 month time period. In a post-hoc analysis of the Speech Pathology reports of individuals with FRDA presented in Study 3 - A videofluoroscopic analysis of swallowing in individuals with FRDA (Chapter 6), the case is made that aspiration seen in FRDA does not necessarily translate to clinical presentation of aspiration-related pneumonia. However, there are acknowledged weaknesses in this method of analysis, and an important next step in this research would be to determine the causal relationship, if any, between dysphagia with concomitant aspiration and the presence of aspiration-related morbidity such as pneumonia.

8.3.1 Recommendations for assessing dysphagia in FRDA

Whilst not a primary aim of this work, the data collected in this research assists to inform best practice in the swallowing assessment of individuals with FRDA. The *Consensus Clinical Management Guidelines for Friedreich ataxia* (Corben et al., 2014) advises individuals with FRDA reporting dysphagia symptoms should to undergo a comprehensive swallowing assessment with a Speech Pathologist, and receive intervention and monitoring when appropriate. These recommendations were based on the best available evidence prior to the publication of the present research.

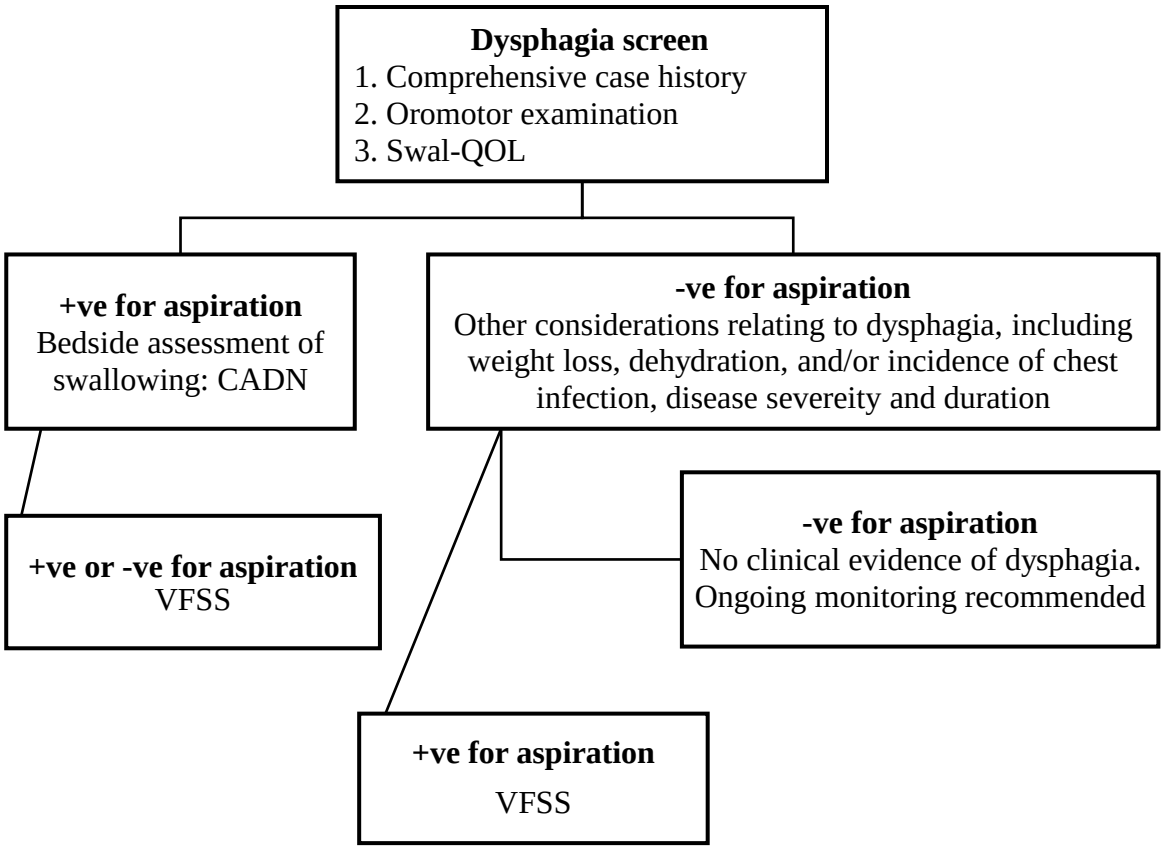
The present body of research reveals that swallowing function and swallowing perception do not correlate in individuals with FRDA, and therefore open-ended questions enquiring about dysphagia during a scheduled clinical visit should not be considered valid. Instead, more informed specific questioning pertaining to swallowing function should be asked, such as those on the Swal-QOL, or via use of a standardised CBE such as the Clinical Assessment of Dysphagia in Neurodegeneration (CADN; Vogel, Rommel, Sauer & Synofzik, 2016). Results of the Swal-QOL will inform the clinician on the impact dysphagia may have on the QOL of the individual, and this information should be used to guide management and rehabilitation of swallowing function.

A bedside examination of swallowing provides valuable information regarding the pre-oral and oral phases of swallowing, including ease of self-feeding and proficiency in transferring and clearing a bolus from the oral cavity. Measures of pharyngeal clearance are also made on bedside assessment but are limited, particularly as the results of this research demonstrate that judgement of aspiration based on the presence or absence of a cough on bedside assessment is unreliable. A recently developed tool, the CADN (Vogel et al., 2016), is a reliable and valid non-instrumental assessment of swallowing designed specifically for use in neurodegenerative conditions. The CADN consists of two parts. In *Part 1: Anamnesis*, the individual is asked seven general questions about their swallowing function relating to the previous 30 days. In *Part 2: Examination with consumption*, the individuals is required to eat and drink four different textures and consistencies, and ratings of swallowing difficulty are made by the clinician (due to the presence of coughing, throat clearing, difficulty chewing or initiating a swallow etc.). Each answer to *Part 1* and each trial in *Part 2* is scored on a scale from 0-no impairment to 4-severe impairment. *Part 1* and *2* are then combined to achieve a total score. With these two scales the CADN is able to provide a comprehensive picture regarding the impact of dysphagia, as well as quantify the severity of the individual's swallowing impairment. The CADN was validated on a cohort of 125 individuals with PD (n=60) and degenerative ataxia (including SCA, FRDA, and autosomal recessive spastic ataxia of Charlevoix-Saguenay; ARSACS) (n=65). Results were compared with Swal-QOL (*Part 1*) and VFSS data (with cut off score of PAS =5 deemed meaningful) (*Part 2*) and validity determined using ROC graphs and correlations. Validity was high with sensitivity of 80% and 84% and specificity 71% and 69% for parts one (*Anamnesis*) and two (*Examination with consumption*) respectively (Vogel et al., 2016).

Instrumental analysis remains the best way to identify aspiration in the FRDA population, however VFSS results alone should not guide recommendations. The application of clinical reasoning is also an important factor in the assessment of individuals with FRDA. Clinical predictors, such as chest status, secretion management, and weight should be taking into consideration in the assessment of dysphagia in individuals with FRDA. (Figure 8-1 Proposed assessment paradigm for aspiration in FRDA). All of factors have been identified as clinical predictors of dysphagia in neurodegenerative disease (Cereda et al., 2014; Coelho et al., 2010; Lam et al., 2007). Further, Disease duration and severity were shown to correlate with dysphagia in this study, and thus individuals with a severe or quickly progressing form of the disease will present with dysphagia. This research also guides timeliness of

assessment, and necessitates the need for close monitoring and repeat assessment of swallowing function, given dysphagia can progress in as little as 12 months.

Figure 8-1 Proposed assessment paradigm for aspiration in FRDA



8.3.2 Recommendations for managing dysphagia in FRDA

The management of FRDA-related dysphagia should be guided and informed via collaboration between the Speech Pathologist, Neurologist, the wider treating team, and the patient, to address the physical and psychosocial impacts of swallowing impairment.

This research revealed oral and pharyngeal dysphagia secondary to FRDA, characterised by reduced bolus control and clearance in the oral phase of swallowing, impaired pharyngeal constriction and clearance, and aspiration (including silent aspiration). Difficulty clearing material from the mouth and pharynx was more pronounced with solid consistencies (biscuit). In some cases, the aspiration observed was trace amounts only, a phenomenon also reported in otherwise healthy individuals (Butler et al., 2010). These data point towards management that includes diet and postural modification, alongside the prescription of

specialised feeding equipment such as controlled-flow containers. Drastic textural modifications to food and thickening fluids is not recommended given the impact dysphagia and these modifications have on the QOL of individuals with FRDA.

8.3.2 Treatment for FRDA-related dysphagia

The data and methods presented in this thesis guides future research into the treatment of FRDA-related dysphagia. The effect of current FRDA treatments (pharmacological and otherwise) on swallowing is unclear (Vogel et al., 2015b). Current practice in FRDA stipulates that dysphagia treatment should be primarily aimed to facilitating safe and satisfactory nutrition and hydration for the individual (Corben et al., 2014). General practices currently include modification of diet and fluids (i.e. softening and moistening of food and thickening of fluids) and using swallowing strategies such as the 'chin tuck' (Vogel, Brown, et al., 2014). Future studies may focus on the following areas:

i. Behavioural treatment

Research in other progressive neurological conditions suggests promising effects of intensive behavioural treatment on dysphagia. In PD, the effect of speech therapy on swallowing has been confirmed in several objective studies. Andrade, Barbosa, Cardoso, and Teive (2006) reported an improvement in laryngeal function after a period of therapy. Improvement in vocal function was also noted. Lee Silvermann Voice Therapy (LSVT); a structured therapy program to treat PD-related dysarthria, has been reported to improve swallowing function (Ramig, Countryman, O'Brien, Hoehn, & Thompson, 1996). The premise of LSVT is to increase vocal effort and enable patients to speak louder. De Angelis and colleagues (1997) reported significant improvements in the swallowing function of 20 individuals with PD following LSVT, as assessed using temporal measures, such as oral and pharyngeal transport time, duration of contact between the base of the tongue and the pharynx, and during velopharyngeal approximation and laryngeal elevation. These results must be interpreted with caution as given the small sample size reported in the study, and lack of longitudinal measure of improvement or maintenance of the gains achieved. The effect of intensive speech therapy to treat dysarthria in FRDA is under researched (Vogel, Folker, et al., 2014). Future research should aim to mitigate this gap in the evidence base, and evaluate the effect of intensive therapy on the swallowing function of individuals with FRDA.

ii. Indirect swallowing strategies

Little evidence exists regarding the effectiveness of indirect swallowing strategies, such as the Masako Manoeuver (Fujiu & Logemann, 1996), the Shaker Exercise (Shaker et al., 2002), and oromotor exercises (outlined in 0). The Masako Manoeuver (whereby the individual is instructed to hold their tongue between their teeth and maintain while swallowing) and the Shaker Exercise (the individual is instructed to lay flat on their back on the floor or bed and hold their head off the floor or bed looking at the feet for a predetermined amount of time) may be difficult to prescribe in the FRDA population given significant motor restrictions. Oromotor exercises are commonly prescribed to individuals with dysphagia in clinical practice, however data pertaining to their effectiveness is lacking (Hind & Robbins, 2013). Argolo and colleagues (2013) investigated the effectiveness of an intensive therapy protocol involving motor swallowing exercises targeting strength and range of motion of the mouth, larynx and pharyngeal structures, as well as coordination between swallowing and breathing, prescribed to individuals with PD (n=15) twice a day, five days a week, for five weeks. A positive impact was seen in swallowing-related QOL (as measured by the Swal-QOL), and improvements were observed in bolus control and oral and pharyngeal residue on VFSS (Argolo, Sampaio, Pinho, Melo, & Nóbrega, 2013). These results were not compared with a control group and therefore results should be considered cautiously. Robbins and colleagues (2007) found the frequency of aspiration was significantly reduced following an eight week treatment program of lingual strengthening in 10 individuals post stroke. Three of this cohort underwent MRI of the tongue, of which two showed increased lingual volume after treatment. Substantial gains were also reported on a dysphagia-related swallowing quality of life questionnaire following treatment (Robbins et al., 2007). Given tongue function is affected by FRDA (Folker et al., 2011) and likely contributes to the oral and pharyngeal residue seen on VFSS in this population, oromotor strengthening targeting the tongue and pharyngeal structures is a worthwhile treatment to investigate.

iii. Biofeedback

Biofeedback, a technique involving visual or auditory references and electromyography, has also been reported to affect physiological swallowing function, and may be useful in the treatment of dysphagia in individuals with FRDA. Biofeedback works on the principle that sensorimotor loss can be compensated for by visual stimuli which allows individuals to assimilate altered function and re-establish functional proprioception (Bogaardt, Grolman, & Fokkens, 2009; Bryant, 1991; de Angelis et al., 1997). In a recent case-control study, Li and colleagues (2016) investigated the use of game-based biofeedback in swallowing therapy in

20 individuals with post-stroke dysphagia, with each participants undergoing one hour sessions three times a week, for a total of 16 sessions. Each session included thirty minutes of traditional swallowing therapy and thirty minutes of laryngeal elevation exercises. The therapy was shown to augment change in hyoid bone movement during swallowing (as measure via ultrasound with a curvilinear transducer) and a functional scale of swallowing (the Functional Oral Intake Scale: FOIS) score (Li et al., 2016).

In PD, the use of video feedback during swallowing therapy has been shown to increase the effectiveness of intervention (Manor, Mootanah, Freud, Giladi, & Cohen, 2013). Manor and colleagues (2013) conducted a RCT whereby 42 individuals with PD and known dysphagia were assigned into either a control group (receiving standard swallowing intervention, including swallowing exercises and compensatory techniques found to be most effective for the individual following FEES assessment) or in the intervention group, who received swallowing therapy with an additional video component. Participants in the research group observed a video of normal swallowing, and then a video of their own disturbed swallowing. During the intervention, the research group were shown videos of their swallowing, and thus were able to observe the effect of compensatory strategies. The swallowing of both groups improved, particularly in terms of pharyngeal residue. No group differences were revealed relating to airway entry during swallowing (penetration and/or aspiration). Improvements on swallowing questionnaires were noted in the intervention group only, suggesting swallowing perception improved with education (Manor et al., 2013). Considering these data, biofeedback has the potential to improve the effectiveness of dysphagia therapy in FRDA, and should be considered in future research.

iv. Surface electrical stimulation (SES)

Use of surface electrical stimulation (SES) to treat dysphagia is an emerging area of research with conflicting results (Baijens et al., 2013; Freed, Freed, Chatburn, & Christian, 2001; Heijnen et al., 2012; Lim, Lee, Lim & Choi, 2009; Ludlow et al., 2007). Baijens and colleagues (2013) investigated the use of SES in a RCT of 90 individuals with PD. The participants were assigned to three groups; group 1 received traditional logopedic dysphagia treatment (consisting of rehabilitative techniques to improve swallowing function and facilitate dietary intake, such as exercises targeting sensorimotor integration and muscle strength) only, group 2 received logopedic therapy with additional motor level SES of the suprahyoid musculature, and group 3 received additional sensory level SES of the suprahyoid musculature. Using FEES and VFSS as outcome measures, the authors identified an

improvement in swallowing in all groups, with no significant or additional influences of SES (Baijens et al., 2013). The same results were found when measuring swallowing-related QOL; whereby the incorporation of SES into dysphagia therapy did not significantly improve swallowing-perception when compared to logopedic therapy in PD (Heijnen et al., 2012). In stroke, SES has been shown to be more effective in the treatment of dysphagia when compared to other methods, such as thermal-tactile stimulation (Freed, Freed, Chatburn, & Christian, 2001), or can work in conjunction with tactile-thermal stimulation to improve the efficacy of dysphagia treatment (Lim, Lee, Lim & Choi, 2009). SES has weak evidence as a sole treatment for neurogenic dysphagia, however may be a useful part of the treatment battery for future work in FRDA-related dysphagia if combined with biofeedback and behavioural treatment.

v. Expiratory muscle strength training (EMST)

Expiratory muscle strength training (EMST) has been proposed as a restorative treatment for dysphagia in individuals with PD (Troche et al., 2010) and may be considered for FRDA Troche and colleagues (2010) conducted a RCT whereby 60 participants with PD completed EMST for 20 minutes a day, five days a week over four weeks. The participants were provided a calibrated or sham handheld EMST device. The active EMST group showed improved swallowing function (based on VFSS) including improvement in scales of penetration and aspiration, as well as improvement in hyolaryngeal function (Troche et al., 2010). Pitts and colleagues (2009) also reported EMST to be beneficial in the treatment of PD-related dysphagia, however did not compare the results to a control group. Despite the perceived benefits of EMST, this technique may be contraindicated in FRDA given that cardiomyopathy is present in many with FRDA and is a contraindication to EMST. EMST involves the build-up of intraoral and intrathoracic pressures (Baker, Davenport, & Sapienza, 2005) and thus may be dangerous for individuals with cardiomyopathy, such is the case in FRDA.

8.4 Future directions

As discussed in Chapter 6, it is likely dysphagia in FRDA is a consequence of mistiming and incoordination of the swallow arising from cerebellar and spinocerebellar degeneration, and is exacerbated by spasticity and weakness. Deficits observed during the oral voluntary phase of the swallow may be related to corticobulbar and corticopontine degeneration (a hallmark feature of FRDA) (Pandolfo, 2009). Diminished pharyngeal and laryngeal sensitivity may be

a manifestation of sensory peripheral neuropathy (also a sequela of FRDA) (Morral, Davis, Qian, Gelman & Koeppen, 2010) and warrants further specific research (outlined below). Functional magnetic resonance imaging (fRMI) has been used previously to determine swallowing neurophysiology in vivo, however can be problematic (Malandraki, Johnson, & Robbins, 2011). fMRI has been previously utilised in neurogenic dysphagia populations, including stroke (Li et al., 2009) and individuals in the early stages of Alzheimer's disease (Humbert et al., 2010). FRDA may pose a significant barrier to this form of assessment given the required positioning whereby participants must lie flat and still for extended periods of time.

Further testing of laryngeal sensitivity and airway protective mechanisms is warranted in the FRDA population given the presence of silent aspiration. Cough reflex testing is one such method and has been reported to correlate with aspirating as identified on VFSS and FEES (Miles et al., 2013). Cough reflex testing involves exposing a person suspected of dysphagia to different concentrations of a cough stimulant (generally citric acid or capsaicin) via a nebulizer and facemask. Measures of cough thresholds are then recorded (Miles et al., 2013). The majority of cough reflex testing research has been conducted in the stroke population with variable results (Guillén-Solà et al., 2015; Miles et al., 2013). Miles and colleagues (2013) reported cough reflex testing was able to identify silent aspiration with 71% sensitivity and 60% specificity using VFSS, and 69% sensitivity and 71% specificity on FEES, whilst Guillén-Solà and colleagyues (2015) reported 19% sensitivity and 71% specificity. Despite these statistics, cough reflex testing may provide valuable information regarding laryngeal sensitivity, and confirm the presence or absence of laryngeal sensorioneuropathy in the disease. Exploration of other objective measures of aspiration, including pulse oximetry, could also enhance the accuracy of aspiration diagnosis. Improving the accuracy of identifying aspiration in FRDA via further exploration of predictability is an important next step. Longitudinal studies are needed to determine the effect of chronic aspiration on respiratory health in individuals with FRDA and the variables impacting on this. Alternative diagnostic outcome measures need to be developed and tested to indicate the effect of aspiration on chest health.

The longitudinal data gathered in this body of research were novel and useful in understanding dysphagia progression in FRDA. A follow-up of individuals over a longer period of time, with the introduction of other health measures (such as the Medical Outcomes

Study Short form (36) Health Survey, Ware Jr & Sherbourne, 1992) would be useful in further informing dysphagia and FRDA progression over time.

8.5 Conclusions

Dysphagia is common in FRDA and can arise at any point during the course of the disease. Further research is required to identify areas of physiological swallowing weakness in FRDA, as well as mapping of the clinical course of FRDA-related dysphagia. Dysphagia significantly affects the QOL of individuals with FRDA and this should be at the forefront of dysphagia management. Intervention should be collaborative between the individual with FRDA and the multidisciplinary team.

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Appendix

Table 0-1 Swal-QOL - Burden (n=59)

	Item	Group	Very much true (1)		Quite a bit true (2)		Somewhat true (3)		A little bit true (4)		Not at all true (5)		Total of participants reporting degree of impairment (score < 5)	
			n	%	n	%	n	%	n	%	n	%	n	%
1	Dealing with my swallowing problem is very difficult	FRDA	0	0	6	10.2	3	5.1	17	28.9	33	55.9	26	44.1
		HC	0	0	0	0	1	1.7	1	1.7	58	9.7	2	3.3
2	My swallowing problem is a major distraction in my life	FRDA	0	0	2	3.4	3	5.1	17	28.8	37	62.7	22	37.3
		HC	0	0	1	1.7	0	0	1	1.7	58	9.7	2	3.3

Table 0-2 Swal-QOL - Eating Desire (n=59)

Item		Group	Very much true (1)		Quite a bit true (2)		Somewhat true (3)		A little bit true (4)		Not at all true (5)		Total of participants reporting degree of impairment (score < 5)	
			n	%	n	%	n	%	n	%	n	%	n	%
1	Most days, I don't care if I eat or not	FRDA	1	1.7	1	1.7	2	3.4	13	22.0	42	71.2	17	28.8
		HC	1	1.7	2	3.3	0	0	3	5.0	54	90	6	10.0
2	I'm rarely hungry anymore	FRDA	4	6.8	1	1.7	5	8.5	7	11.9	42	71.2	17	28.8
		HC	0	0	1	1.7	3	5.0	5	8.3	51	85.0	9	15.0
3	I don't enjoy eating anymore	FRDA	0	0	1	1.69	3	6.78	5	8.47	50	84.8	9	15.5
		HC	1	1.7	0	0	0	0	3	3.3	56	93.3	4	6.7

Table 0-3 Swal-QOL - Eating Duration (n=59)

	Item	Group	Very much true (1)		Quite a bit true (2)		Somewhat true (3)		A little bit true (4)		Not at all true (5)		Total of participants reporting degree of impairment (score < 5)	
			n	%	n	%	n	%	n	%	n	%	n	%
1	It takes me longer to eat than other people	FRDA	10	16.9	8	13.6	14	23.7	13	22.0	14	23.7	45	76.27
		HC	0	0	2	3.3	1	1.7	7	11.7	50	83.3	10	16.7
2	It takes me forever to eat a meal	FRDA	3	5.1	6	10.2	10	16.9	14	23.7	26	61.0	33	55.6
		HC	0	0	1	1.7	0	0	2	3.3	57	95.0	3	5.0

Table 0-4 Swal-QOL - Symptom Frequency (n=59)

	Item	Group	Almost always (1)		Often (2)		Sometimes (3)		Hardly ever (4)		Never (5)		Total of participants reporting degree of impairment (score < 5)	
			n	%	n	%	n	%	n	%	n	%	n	%
1	Coughing	FRDA	1	1.7	7	11.9	28	47.6	15	25.4	8	13.6	51	86.4
		HC	0	0	0	0	7	11.7	20	33.3	33	55.0	27	45.0
2	Choking when you eat food	FRDA	0	0	3	5.1	19	32.2	19	32.2	18	30.5	41	69.5
		HC	0	0	0	0	2	3.3	11	18.3	47	78.3	13	21.7
3	Chocking when you take liquids	FRDA	0	0	3	5.1	23	39.0	18	30.5	15	25.4	44	74.6
		HC	0	0	0	0	1	1.7	15	25.0	44	73.3	15	25.4
4	Having thick saliva of phlegm	FRDA	0	0	3	5.1	13	22.0	16	27.1	27	45.8	32	54.2
		HC	0	0	2	3.3	2	3.3	6	10.0	50	83.3	10	16.7
5	Gagging	FRDA	1	1.7	2	3.4	9	15.3	18	30.5	29	49.2	30	50.9
		HC	0	0	0	0	0	0	4	6.7	56	93.3	4	6.7
6	Drooling	FRDA	0	0.0	3	5.1	10	17.0	20	33.9	26	44.1	33	55.9

		HC	0	0	0	0	0	0	7	11.7	53	88.3	7	11.7
7	Problems chewing	FRDA	1	1.7	0	0.0	11	18.6	12	20.3	35	59.3	24	40.7
		HC	0	0	0	0	0	0	2	3.3	58	96.7	2	3.3
8	Having excess saliva or phlegm	FRDA	0	0.0	1	1.7	17	28.8	12	20.3	29	49.2	30	50.9
		HC	0	0	1	1.7	1	1.7	6	10.0	52	86.7	8	13.3
9	Having to clear your throat	FRDA	2	3.4	4	6.8	22	37.3	17	28.8	14	23.7	45	76.3
		HC	0	0	3	5.0	9	15.0	14	23.3	34	56.7	26	43.3
10	Food sticking in your throat	FRDA	1	1.7	0	0	15	25.4	15	25.4	28	47.5	31	52.5
		HC	0	0	0	0	2	3.3	10	16.7	48	80.0	12	20.0
11	Food sticking in your mouth	FRDA	1	1.7	0	0	14	23.7	12	20.3	32	54.2	27	45.8
		HC	0	0	0	0	2	3.3	8	13.3	50	83.3	10	16.7

12	Food or liquid dribbling out of your mouth	FRDA	0	0	0	0	10	17.0	16	27.1	33	55.9	26	44.1
		HC	0	0	0	0	1	1.7	3	5.0	56	93.3	4	6.7
13	Food or liquid coming out of your nose	FRDA	0	0	1	1.7	2	3.4	13	22.0	43	72.9	16	27.1
		HC	0	0	0	0	0	0	2	3.3	58	96.7	2	3.3
14	Coughing food or liquid out of your mouth when it gets stuck	FRDA	0	0	2	3.4	15	25.4	15	25.4	27	45.8	32	54.2
		HC	0	0	0	0	0	0	7	11.7	53	88.3	7	11.7

Table 0-5 Swal-QOL - Food Selection (n=59)

	Item	Group	Strongly agree (1)		Agree (2)		Uncertain (3)		Disagree (4)		Strongly disagree (5)		Total of participants reporting degree of impairment (score < 5)	
			n	%	n	%	n	%	n	%	n	%	n	%
1	Figuring out what I can and can't eat is a problem for me	FRDA	0	0	5	8.5	3	5.1	11	18.6	40	67.8	19	32.2
		HC	0	0	1	1.7	0	0	1	1.7	58	96.7	2	3.3
2	It is difficult to find foods that I both like and can eat	FRDA	0	0	1	1.7	1	1.7	12	20.3	45	76.3	14	23.7
		HC	0	0	0	0	2	3.3	1	1.7	57	95.0	3	5.0

Table 0-6 Swal-QOL - Communication (n=59)

	Item	Group	All of the time (1)		Most of the time (2)		Some of the time (3)		A little of the time (4)		None of the time (5)		Total of participants reporting degree of impairment (score < 5)	
			n	%	n	%	n	%	n	%	n	%	n	%
1	People have a hard time understanding me	FRDA	0	0	3	5.1	20	33.9	17	28.8	19	32.2	40	67.8
		HC	0	0	0	0	0	0	2	3.3	58	96.7	2	3.3
2	It’s been difficult for me to speak clearly	FRDA	0	0	3	5.1	13	22.03	21	35.6	22	37.29	37	62.7
		HC	0	0	0	0	0	0	1	1.7	59	98.3	1	1.7

Table 0-7 Swal-QOL - Fear (n=59)

	Item	Group	Almost always (1)		Often (2)		Sometimes (3)		Hardly ever (4)		Never (5)		Total of participants reporting degree of impairment (score < 5)	
			n	%	n	%	n	%	n	%	n	%	n	%
1	I fear I may start choking when I eat food	FRDA	1	1.7	2	3.4	11	18.6	15	25.4	30	50.8	29	49.15
		HC	0	0	0	0	1	1.7	3	5.0	56	93.3	4	6.7
2	I worry about getting pneumonia	FRDA	0	0	2	3.4	4	6.8	8	13.6	45	76.3	14	23.73
		HC	0	0	0	0	1	1.7	2	3.3	57	95.0	3	5.0
3	I am afraid of choking when I drink liquids	FRDA	1	1.7	5	8.5	12	20.3	16	27.1	25	42.4	34	57.63
		HC	0	0	0	0	0	0	4	6.7	56	93.3	4	6.7
4	I never know when I am going to choke	FRDA	4	6.8	7	11.9	14	23.7	11	18.6	23	39.0	36	61.0
		HC	0	0	0	0	1	1.7	2	3.3	57	95.0	3	5.0

Table 0-8 Swal-QOL - Mental Health (n=59)

Item		Group	Always true (1)		Often true (2)		Sometimes true (3)		Hardly ever true (4)		Never true (5)		Total of participants reporting degree of impairment (score < 5)	
			n	%	n	%	n	%	n	%	n	%	n	%
1	My swallowing problem depresses me	FRDA	0	0.00	0	0.00	3	5.08	12	20.34	44	74.58	15	25.42
		HC	0	0	0	0	0	0	1	1.7	59	98.3	1	1.7
2	Having to be so careful when I eat or drink annoys me	FRDA	2	3.39	0	0.00	12	20.34	17	28.81	28	47.46	31	52.5
		HC	0	0	0	0	0	0	1	1.7	59	98.3	1	1.7
3	I’ve been discouraged by my swallowing problem	FRDA	0	0.00	1	1.69	5	8.47	13	22.03	40	67.80	19	32.2
		HC	0	0	0	0	0	0	1	1.7	59	98.3	1	1.7
4	My swallowing problem frustrates me	FRDA	1	1.69	2	3.39	10	16.95	10	16.95	36	61.02	23	38.98
		HC	0	0	0	0	0	0	2	3.3	58	96.7	2	3.3

5	I get impatient dealing with my swallowing problem	FRDA	2	3.39	2	3.39	7	11.86	7	11.86	41	69.49	18	30.51
		HC	0	0	0	0	0	0	1	1.7	59	98.3	1	1.7

Table 0-9 Swal-QOL - Social (n=59)

	Item	Group	Strongly agree (1)		Agree (2)		Uncertain (3)		Disagree (4)		Strongly disagree (5)		Total of participants reporting degree of impairment (score < 5)	
			n	%	n	%	n	%	n	%	n	%	n	%
1	I do not go out to eat because of my swallowing problem	FRDA	0	0	4	6.8	1	1.7	9	15.2	45	76.3	14	23.7
		HC	0	0	0	0	0	0	1	1.7	59	98.3	1	1.7
2	My swallowing problem makes it hard to have a social life	FRDA	0	0	3	5.08	2	3.39	7	11.9	47	79.7	12	20.3
		HC	0	0	0	0	0	0	2	3.3	58	96.7	2	3.3
3	My usual work or leisure activities have changed because of my swallowing problem	FRDA	0	0	1	1.69	3	5.08	8	13.6	47	79.7	12	20.3
		HC	0	0	0	0	0	0	1	1.7	59	98.3	1	1.7
4		FRDA	0	0.00	1	1.69	3	5.08	7	11.9	48	81.4	11	18.6

	Social gatherings (like holidays or get-togethers) are not enjoyable because if my swallowing problem	HC	0	0	0	0	0	0	1	1.7	59	98.3	1	1.7
5	My role with family and friends has changed because of my swallowing problem	FRDA	0	0.00	1	1.69	1	1.69	8	13.6	49	83.1	10	16.9
		HC	0	0	0	0	0	0	1	1.7	59	98.3	1	1.7

Table 0-10 Swal-QOL - Fatigue (n=59)

	Item	Group	All of the time (1)		Most of the time (2)		Some of the time (3)		A little of the time (4)		None of the time (5)		Total of participants reporting degree of impairment (score < 5)	
			n	%	n	%	n	%	n	%	n	%	n	%
1	Feel weak?	FRDA	2	3.4	6	10.2	18	30.5	13	22.0	20	33.9	39	66.1
		HC	0	0	0	0	5	8.3	14	23.3	41	68.3	9	15.0
2	Feel tired?	FRDA	5	8.5	16	27.1	15	25.4	13	22.0	10	16.9	49	83.1
		HC	0	0	3	6.0	19	31.7	22	36.7	16	26.7	44	73.3
3	Feel exhausted?	FRDA	4	6.8	9	15.2	23	39.0	10	16.9	13	22.0	46	78.0
		HC	0	0	1	1.7	11	18.3	20	33.3	28	46.7	32	53.3

Table 0-11 Swal-QOL - Sleep (n=59)

	Item	Group	All of the time (1)		Most of the time (2)		Some of the time (3)		A little of the time (4)		None of the time (5)		Total of participants reporting degree of impairment (score < 5)	
			n	%	n	%	n	%	n	%	n	%	n	%
1	Have trouble falling asleep?	FRDA	2	3.39	6	10.2	18	30.5	13	22.0	20	33.9	39	66.1
		HC	1	1.7	0	0	7	11.7	24	40.0	28	46.7	32	53.3
2	Have trouble staying asleep?	FRDA	5	8.5	16	27.1	15	25.4	14	22.0	10	16.9	50	84.7
		HC	0	0	1	1.7	9	15.0	0	0	35	58.3	25	41.7

Table 5-1 FDA-2 Reflexes - Cough (n=35)

Score	Severity	n	%
1	Normal	1	22.9
2-4	Mild	22	62.9
5-6	Moderate	3	8.6
7-8	Severe	2	5.7
9	Maximally impaired	0	0

Table 5-2 FDA-2 Reflexes - Swallow (n=35)

Score	Severity	n	%
1	Normal	7	20.0
2-4	Mild	17	48.6
5-6	Moderate	11	31.42
7-8	Severe	0	0
9	Maximally impaired	0	0

Table 5-3 FDA-2 Reflexes - Dribble/drool (n=35)

Score	Severity	n	%
1	Normal	22	62.9
2-4	Mild	9	25.7
5-6	Moderate	4	11.4
7-8	Severe	0	0
9	Maximally impaired	0	0

Table 5-4 FDA-2 Respiration - At rest (n=35)

Score	Severity	n	%
1	Normal	10	28.6
2-4	Mild	19	54.3
5-6	Moderate	4	11.4
7-8	Severe	2	5.7
9	Maximally impaired	0	0

Table 5-5 FDA-2 Respiration - In speech (n=35)

Score	Severity	n	%
1	Normal	9	25.7
2-4	Mild	21	6.0
5-6	Moderate	4	11.4
7-8	Severe	1	2.9
9	Maximally impaired	0	0

Table 5-6 FDA-2 Lips - at rest (n=35)

Score	Severity	n	%
1	Normal	31	88.6
2-4	Mild	4	11.4
5-6	Moderate	0	0
7-8	Severe	0	0
9	Maximally impaired	0	0

Table 5-7 FDA-2 Lips - Spread (n=35)

Score	Severity	n	%
1	Normal	31	88.6
2-4	Mild	4	11.4
5-6	Moderate	0	0
7-8	Severe	0	0
9	Maximally impaired	0	0

Table 5-8 FDA-2 Lips - Seal (n=35)

Score	Severity	n	%
1	Normal	11	31.4
2-4	Mild	19	54.3
5-6	Moderate	5	14.3
7-8	Severe	0	0
9	Maximally impaired	0	0

Table 5-9 FDA-2 Lips – Alternate (n=35)

Score	Severity	n	%
1	Normal	3	8.6
2-4	Mild	27	77.1
5-6	Moderate	5	14.3
7-8	Severe	0	0
9	Maximally impaired	0	0

Table 5-10 FDA-2 Lips - In speech (n=35)

Score	Severity	n	%
1	Normal	4	11.4
2-4	Mild	25	71.4
5-6	Moderate	6	17.1
7-8	Severe	0	0
9	Maximally impaired	0	0

Table 5-11 FDA-2 Palate - Fluids (n=35)

Score	Severity	n	%
1	Normal	31	88.6
2-4	Mild	4	11.4
5-6	Moderate	0	0
7-8	Severe	0	0
9	Maximally impaired	0	0

Table 5-12 FDA-2 Palate - Maintenance (n=35)

Score	Severity	n	%
1	Normal	31	88.6
2-4	Mild	4	11.4
5-6	Moderate	0	0
7-8	Severe	0	0
9	Maximally impaired	0	0

Table 5-13 FDA-2 Palate - In speech (n=35)

Score	Severity	n	%
1	Normal	4	11.4
2-4	Mild	23	65.7
5-6	Moderate	8	22.9
7-8	Severe	0	0
9	Maximally impaired	0	0

Table 5-14 FDA-2 Laryngeal - Time (n=35)

Score	Severity	n	%
1	Normal	13	37.1
2-4	Mild	9	25.7
5-6	Moderate	11	31.4
7-8	Severe	1	2.9
9	Maximally impaired	1	2.9

Table 5-15 FDA-2 Laryngeal - Pitch (n=35)

Score	Severity	n	%
1	Normal	4	11.4
2-4	Mild	10	28.6
5-6	Moderate	8	22.9
7-8	Severe	12	34.3
9	Maximally impaired	1	2.9

Table 5-16 FDA-2 Laryngeal - Volume (n=35)

Score	Severity	n	%
1	Normal	3	8.6
2-4	Mild	10	28.6
5-6	Moderate	11	31.4
7-8	Severe	11	31.4
9	Maximally impaired	0	0

Table 5-17 FDA-2 Laryngeal - In speech (n=35)

Score	Severity	n	%
1	Normal	6	17.1
2-4	Mild	20	57.1
5-6	Moderate	7	2.0
7-8	Severe	2	5.7
9	Maximally impaired	0	0

Table 5-18 FDA-2 Tongue - At rest (n=35)

Score	Severity	n	%
1	Normal	18	51.4
2-4	Mild	14	40
5-6	Moderate	3	8.6
7-8	Severe	0	0
9	Maximally impaired	0	0

Table 5-19 FDA-2 Tongue - Protrusion (n=35)

Score	Severity	n	%
1	Normal	16	45.7
2-4	Mild	8	22.9
5-6	Moderate	9	25.7
7-8	Severe	2	5.7
9	Maximally impaired	0	0

Table 5-20 FDA-2 Tongue - Elevation (n=35)

Score	Severity	n	%
1	Normal	10	28.6
2-4	Mild	15	42.9
5-6	Moderate	7	20.0
7-8	Severe	3	8.6
9	Maximally impaired	0	0

Table 5-21 FDA-2 Tongue - Lateral (n=35)

Score	Severity	n	%
1	Normal	18	51.4
2-4	Mild	10	28.6
5-6	Moderate	6	17.1
7-8	Severe	1	2.9
9	Maximally impaired	0	0

Table 5-22 FDA-2 Tongue - Alternate (n=35)

Score	Severity	n	%
1	Normal	4	11.4
2-4	Mild	17	48.6
5-6	Moderate	12	34.3
7-8	Severe	2	5.7
9	Maximally impaired	0	0

Table 5-23 FDA-2 Tongue - In speech (n=35)

Score	Severity	n	%
1	Normal	3	8.6
2-4	Mild	18	51.4
5-6	Moderate	14	40.0
7-8	Severe	0	0
9	Maximally impaired	0	0

Table 5-24 FDA-2 Intelligibility - Words (n=35)

Score	Severity	n	%
1	Normal	18	51.4
2-4	Mild	11	31.4
5-6	Moderate	6	17.1
7-8	Severe	0	0
9	Maximally impaired	0	0

Table 5-25 FDA-2 Intelligibility - Sentences (n=35)

Score	Severity	n	%
1	Normal	15	42.9
2-4	Mild	12	37.1
5-6	Moderate	6	17.1
7-8	Severe	1	2.9
9	Maximally impaired	0	0

Table 5-26 FDA-2 Intelligibility - Conversation (n=35)

Score	Severity	n	%
1	Normal	13	37.1
2-4	Mild	18	51.4
5-6	Moderate	3	8.6
7-8	Severe	1	2.9
9	Maximally impaired	0	0

Table 5-27 Swal-QOL at TP1 and TP2 by individual

	Burden		*Eating desire*		*Eating duration*		*Symptom frequency*		*Food selection*		*Communication*		*Fear*		*Mental Health*		*Social*		*Fatigue*		*Sleep*		*Total*	
	TP1	TP2	TP1	TP2	TP1	TP2	TP1	TP2	TP1	TP2	TP1	TP2	TP1	TP2	TP1	TP2	TP1	TP2	TP1	TP2	TP1	TP2	TP1	TP2
FA002	6	7	14	15	4	4	41	39	7	9	6	7	14	15	18	19	25	25	9	9	6	6	150	155
FA005	10	10	15	15	10	10	66	59	10	10	10	10	17	19	25	25	25	25	12	12	10	10	210	205
FA006	10	10	15	15	9	8	62	60	8	9	8	8	16	15	25	25	24	25	10	8	9	10	196	193
FA007	8	6	10	14	5	2	52	46	10	10	6	4	12	17	14	22	16	25	3	15	2	8	138	169
FA012	10	10	15	15	7	3	61	63	7	10	6	8	15	19	24	25	25	25	14	15	10	10	194	203
FA013	10	10	15	13	6	7	52	49	10	9	8	8	11	15	21	23	25	25	8	15	5	10	171	184
FA015	4	6	12	14	6	6	48	45	5	6	6	5	13	15	16	17	16	20	10	9	8	7	144	150
FA016	9	9	11	15	8	7	60	63	10	10	7	8	16	18	21	24	25	25	14	13	9	9	190	201
FA029	10	10	15	15	10	10	63	60	10	10	10	10	19	17	25	25	25	25	4	6	5	8	196	196
FA032	10	10	13	12	8	3	64	49	10	10	10	6	20	18	25	24	25	25	12	12	9	8	206	177

FA034	4	4	5	4	2	2	30	19	4	4	7	6	6	5	9	8	13	9	3	3	2	2	85	66
FA039	10	10	15	15	10	10	70	65	10	10	10	8	20	20	25	25	25	25	15	15	10	10	220	213
FA046	10	10	15	15	4	4	66	62	8	10	10	6	20	19	25	21	22	22	10	9	6	8	196	186
FA048	10	6	11	12	9	6	46	48	8	10	8	6	17	16	22	23	25	25	12	9	7	7	175	168
FA050	8	9	15	15	8	8	47	43	8	8	10	8	11	10	19	18	25	25	7	9	4	6	162	159
FA051	10	10	15	15	10	10	59	70	10	10	8	10	20	20	25	25	25	25	9	15	5	10	196	220
FA052	10	9	11	10	7	8	56	56	9	10	9	8	18	17	25	25	22	25	9	12	8	7	184	187

Table 5-28 FDA-2 domain and total mean scores at TP1 and TP2 by individual (n=9)

	Reflexes		*Respiration*		*Lips*		*Palate*		*Laryngeal*		*Tongue*		*Intelligibility*		*Total*	
	TP1	TP2	TP1	TP2	TP1	TP2	TP1	TP2	TP1	TP2	TP1	TP2	TP1	TP2	TP1	TP2
FA001	2.33	3.33	2.50	3.00	2.00	2.40	1.67	2.33	3.50	4.75	2.00	3.00	1.00	3.00	56	81
FA015	3.67	4.33	3.00	3.00	3.00	3.00	3.00	3.00	5.50	6.50	3.67	4.67	3.00	3.00	94	106
FA016	3.00	3.00	3.00	2.00	2.20	2.20	1.67	1.67	3.00	5.00	2.33	2.17	1.00	3.00	60	71
FA029	3.67	2.33	4.00	3.00	2.60	2.20	1.67	1.67	4.00	3.50	3.67	2.67	3.00	3.00	84	68
FA032	1.00	3.67	2.00	4.00	2.60	2.20	1.67	2.33	2.50	3.25	2.67	2.83	1.00	3.00	54	76
FA037	2.33	3.67	2.00	4.00	2.20	2.40	1.67	2.67	4.00	4.00	4.33	3.33	2.33	3.67	76	86
FA047	3.67	5.00	3.00	5.00	2.60	3.80	3.67	4.33	6.00	6.50	3.67	4.33	3.67	3.00	118	118
FA048	3.00	3.33	4.00	4.00	2.20	2.60	2.33	3.00	6.00	5.00	3.00	3.17	3.00	3.00	86	88
FA054	2.33	1.67	2.00	2.50	1.80	2.20	1.67	1.67	3.00	3.00	2.33	2.00	1.67	1.00	56	53

Table 5-29 VFSS results scores at TP1 and TP2 by individual - BAS Oral Phase parameters (n=12)

	Lip function						Tongue function						Jaw Function						Soft Palate elevation					
	Fluid		Puree		Biscuit		Fluid		Puree		Biscuit		Fluid		Puree		Biscuit		Fluid		Puree		Biscuit	
ID	TP 1	TP 2	TP 1	TP 2	TP 1	TP 2	TP 1	TP 2	TP 1	TP 2	TP 1	TP 2	TP 1	TP 2	TP 1	TP 2	TP 1	TP 2	TP 1	TP 2	TP 1	TP 2	TP 1	TP 2
FA001	1	2	1	2	1	2	1	1	1	2	2	3	1	1	1	1	1	1	2	1	2	1	3	1
FA005	1	1	1	2	1	2	1	1	1	2	2	3	1	1	1	1	1	1	1	1	1	1	1	1
FA015	1	1	1	2	1	2	1	2	2	4	4	4	1	1	1	1	1	1	4	3	4	3	4	3
FA016	1	1	1	2	1	2	1	2	2	3	2	3	1	1	1	1	1	1	1	1	1	1	1	1
FA021	2	1		2	2	1	2	2		3	3	4	1	1		1	2	1	2	3		3	2	3
FA029	1	1	1	2	1	1	2	1	3	2	2	3	1	1	1	1	1	1	1	2	1	2	1	2
FA032	1	1	2	1	2	1	1	1	1	2	2	2	2	1	1	1	1	1	2	2	2	2	2	2
FA037	1	1	1	1	1	1	3	1	2	2	3	3	1	1	1	1	1	1	1	2	1	2	1	2
FA039	1	1	1	2	1	2	2	1	1	2	4	4	1	1	1	1	1	1	1	1	1	1	1	1
FA046	2	1	2	2	2	2	2	1	3	2	3	3	1	1	1	2	1	2	3	3	4	3	4	3
FA048	1	1	1	1	1	1	1	2	2	2	3	3	1	1	1	1	1	1	2	2	2	2	2	2
FA054	1	1	2	1	2	1	1	1	3	2	3	2	1	1	1	1	1	1	1	1	1	1	1	1

Table 5-30 VFSS results scores at TP1 and TP2 by individual - BAS Pharyngeal Phase parameters (n=12)

	Reflex initiation						Aspiration						Residue in valleculae						Residue in pyriform sinuses						Pharyngeal Function						Cricopharyngeal function					
	F		P		B		F		P		B		F		P		B		F		P		B		F		P		B		F		P		B	
ID	TP1	TP2	TP1	TP2	TP1	TP2	TP1	TP2	TP1	TP2	TP1	TP2	TP1	TP2	TP1	TP2	TP1	TP2	TP1	TP2	TP1	TP2	TP1	TP2	TP1	TP2	TP1	TP2	TP1	TP2	TP1	TP2	TP1	TP2	TP1	TP2
FA001	2	2	2	2	2	2	1	1	1	1	1	1	1	1	2	4	2	4	1	1	1	2	1	3	1	1	1	3	1	3	1	1	1	3	1	3
FA005	2	3	3	3	3	3	1	2	1	1	1	1	1	2	1	3	3	4	1	1	1	2	2	2	1	1	1	2	3	2	1	1	1	2	2	3
FA015	3	4	3	3	3	3	2	4	2	2	1	1	1	2	2	3	4	4	1	2	2	2	2	2	1	3	3	3	3	3	1	3	3	3	3	3
FA016	2	3	3	3	3	3	1	2	2	1	1	1	2	2	3	3	2	3	1	1	2	2	2	2	1	1	2	2	2	2	1	1	3	2	2	2
FA021	4	4		4	4	4	3	3		2	2	3	3	3		4	4	4	3	3		3	3	4	3	2		3	3	4	3	2		3	4	4
FA029	3	3	3	4	3	3	1	4	3	4	1	1	2	2	4	3	3	3	1	2	3	2	1	2	1	2	3	3	1	3	2	2	3	2	1	2
FA032	3	4	3	3	3	3	1	3	2	2	1	1	1	1	2	2	3	2	1	1	2	2	2	2	1	1	2	2	2	2	1	1	2	2	2	2
FA037	3	3	3	3	3	3	2	2	2	3	1	1	1	2	2	4	3	4	1	1	1	2	2	2	1	1	1	3	2	3	1	1	1	2	2	2
FA039	3	3	3	3	3	3	1	3	1	1	1	1	1	1	3	3	4	4	1	1	2	2	1	2	1	1	3	2	3	3	1	1	3	3	4	4
FA046	4	4	4	4	4	4	3	3	2	2	2	1	3	2	3	4	3	4	2	2	3	3	3	3	2	2	3	4	3	4	2	2	2	4	2	4

FA048	3	3	3	3	3	3	2	3	1	1	1	1	1	1	3	3	4	3	1	1	3	2	2	2	1	1	2	2	2	2	1	1	3	2	3	2
FA054	3	4	3	3	3	3	2	2	3	2	2	1	1	1	1	2	1	2	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1

F – Fluid, P – Puree, B- Biscuit, TP1 – Time point 1, TP2 – Time point 2

Table 5-31 VFSS results scores at TP1 and TP2 by individual - PAS score (n=12)

Participant ID	Fluid		Puree		Biscuit	
	TP1	TP2	TP1	TP2	TP1	TP2
FA001	1	1	1	1	1	1
FA005	1	2	1	1	1	1
FA015	2	7	2	2	1	1
FA016	1	2	2	1	1	1
FA021	8	8			4	8
FA029	1	8	8	8	1	1
FA032	1	7	2	2	1	1
FA037	2	2	2	4	1	1
FA039	1	8	1	1	1	1
FA046	8	8	4	4	4	8
FA048	4	7	1	1	1	1
FA054	4	2	8	2	4	1