**Receiving Enzyme Replacement Therapy for a Lysosomal Storage Disorder:
A Preliminary Exploration of the Experiences of Young Patients and their Families.**

R. Freedman¹, M. Sahhar^{1,2}, L. Curnow², J. Lee^{2,3}, H. Peters.^{2,3}

¹ Master of Genetic Counselling, Dept of Paediatrics, Faculty of Medicine, Dentistry and Health Sciences,
University of Melbourne, Victoria, Australia

² Genetic Health Services Victoria, Victoria Australia

³ Metabolic Unit, Murdoch Children's Research Institute, Royal Children's Hospital, Flemington Road Parkville,
Victoria, Australia

Contact: Rebecca Freedman

Ph: 61 08 9340 1525 **Fax:** 61 08 9340 1678

Email: rebeccafreedman@health.wa.gov.au

Postal Address:

Genetic Services of Western Australia
Level Four, Agnes Walsh House,
King Edward Memorial Hospital
374 Bagot Road
Subiaco, Western Australia 6008

ABSTRACT

For lysosomal storage disorders medical intervention becomes part of life, shaping the reality of the condition for affected individuals and families. Enzyme replacement therapy (ERT) is available to treat some lysosomal storage disorders. ERT is costly and time consuming, requiring frequent hospital visits to receive intravenous infusions. This qualitative study sought to explore the impact of receiving ERT for a lysosomal storage disorder on the health related quality of life (HRQoL) of young patients and their families. Fifteen semi-structured interviews were conducted with young people and parents and siblings of young people accessing ERT for Pompe disease, Gaucher disease or mucopolysaccharidosis types I or II living in Victoria, Australia. Interviews were transcribed then analyzed thematically. The biopsychosocial model assisted in interpreting themes. Findings revealed positive attitudes towards ERT, with noticed improvements in physical and psychosocial well-being. Participants prioritised intervention over other activities and provided suggestions for improving current service delivery. Communication with family members and professionals was deemed important, especially in respect to information provision. Participants described challenges associated with living with a lysosomal storage disorder and receiving ERT and coping strategies, such as positive thinking and ways to manage uncertainty. These findings provide valuable insights into the impact of living with a chronic genetic condition and receiving intensive treatment on HRQoL.

Key Words: lysosomal storage disorder, enzyme replacement therapy, health related quality of life, biopsychosocial model, young people, families, mucopolysaccharidosis, Gaucher, Pompe.

INTRODUCTION

The lysosomal storage disorders comprise a large group of inborn errors of metabolism that often affect young people. Most lysosomal storage disorders are caused by an absence or deficiency of specific lysosomal enzymes responsible for the degradation of a specific lipid or carbohydrate within the cells of the body (Deegan & Cox, 2009; Wilcox, 2004). Without these enzymes, the substrate accumulates in the

cells, impeding normal functioning and upsetting metabolic pathways. Lysosomal storage disorders are multi-systemic and progressive (Coman et al., 2008; Deegan & Cox, 2009; Muenzer, 2004; Wilcox, 2004). Table 1 illustrates the clinical features of the conditions represented in this study.

In Australia enzyme replacement therapy (ERT) is now available to treat MPS I, II and VI, Pompe, type 1 Gaucher and Fabry diseases (Australian Government Department on Health and Ageing [ADGHA] 2010a,b,c,d,e; Beck, 2007; Brady & Schiffmann, 2004). Imiglucerase (Cerezyme[®]) has been subsidised by the Life Saving Drugs Programme (LSDP) for patients with type 1 Gaucher disease since 1995 (AGDHA, 2010e). Prior to the availability of ERT, treatment for Gaucher consisted of pain management, surgery for bone fractures and avascular necrosis, splenectomy for thrombocytopenia and blood transfusions for anaemia. Those with very severe presentations received bone marrow transplantations; however, this was associated with morbidity and mortality (AGDHA, 2010e). The success of enzyme therapy for treating Gaucher disease lead to the development of ERT for treating other disorders. Laronidase (Aldurazyme[®]) has been subsidised by the LSDP since 2007 and Idursulfase (Elaprase[®]) since 2008 to treat the non-neurological features of MPSI and MPSII, respectively (AGDHA, 2010b,c). Care before this time involved the management of cardiac, otolaryngological, ophthalmological and orthopaedic manifestations. Bone marrow transplantations or hematopoietic stem cell transplantations (HSCT) were performed for patients with MPSI (Pitt & Lavery, 2009). These may still be accessed by some in adjunct with ERT (AGDHA, 2010b; Wynn et al., 2009). Prior to the advent of ERT for infantile onset Pompe disease, treatment was palliative. In 2010, the LSDP began subsidising Alglucosidase alfa (Myozyme[®]); however some patients had received this earlier by other means (AGDHA, 2010d).

Table I: Features of MPS I and II, Gaucher Disease and Pompe Disease

LSD (Group)	Deficient Enzyme & Accumulated Product	Mode of inheritance	Summary of main clinical features typically seen in untreated patients.	Age of onset	Incidence	References
MPS I The mucopoly-saccharidoses	α -iduronidase <i>Mucopoly-saccharides</i> also called <i>glycosaminoglycans</i> (GAGs) accumulate within the cells.	Autosomal Recessive	<ul style="list-style-type: none">Coarsening of facial features worsens over timeHepatosplenomegaly causing protruding abdomenShort stature, skeletal dysplasia, scoliosis, joint contractures and muscle weaknessCardiovascular issuesRespiratory issues, e.g., airway obstruction, sleep apneaHearing loss,Visual impairments, corneal cloudingNeurological involvement in some patients (e.g. intellectual disability)	Severe: Mean age of onset is 9 months. Attenuated: Diagnoses usually made between 3 and 10 years of age	Estimated for each single MPS disease 1:100 000	Bailey (2008); Clarke & Heppner (2011); Muenzer (2004); Pitt, Lavery & Wager, (2009); Wilcox (2004)
MPS II The mucopoly-saccharidoses	Iduronate sulphatase GAGs accumulate within the cells.	X linked	<ul style="list-style-type: none">Progressive coarsening of the facial featuresHepatosplenomegalyShort stature, skeletal dysplasia, scoliosis, joint contractures and muscle weaknessCardiovascular issuesRespiratory issues, e.g., airway obstruction, sleep apneaMacroglossiaHearing loss, recurrent otitis mediaVisual impairments, however corneal clouding is not usually observedCNS involvement seen in severe but generally not in attenuated forms, some may experience mild-moderate learning difficulties	Between 18 months and four years Attenuated forms often diagnosed later	Estimated for each single MPS disease 1:100 000	Bailey (2008); Muenzer (2004); Scarpa (2011); Schulze-Frenking et al. (2011)
Gaucher Disease (The sphingolipidoses)	Glucocerebrosidase <i>glucoceramide</i> accumulates	Autosomal Recessive	<div>Type I<ul style="list-style-type: none">Progressive hepatosplenomegaly with resultant anaemia and thrombocytopenia (low blood platelet count)Bone disease with acute bone crises, fractures and osteoporosisPain is often reported and can be debilitating<div>Type II and III<ul style="list-style-type: none">Characterised by neurological involvement, with a progressive neurodegenerative disorder</div></div>	Any age Infancy or early childhood	1/50 000 live births in the general and 1/450 - 1000 live births in Ashkenazi Jewish Population	Bailey (2008); Brady & Schiffmann (2004); Deegan & Cox (2010); Packman et al. (2010); Pastores & Hughes(2008)

			in type II			
Pompe	α -glucosidase	Autosomal Recessive	Pompe - Classic Infantile Onset <ul style="list-style-type: none">Progressive muscle disease and feeding difficulties causing failure to thriveMuscle weaknessHypotoniaCardiomegaly & hypertrophic cardiomyopathy.Many infants die from cardio- respiratory failure by 12 to 24 months Non-classic infantile and late onset Pompe <ul style="list-style-type: none">Progressive muscle weakness, often involving respiratory muscles leading to respiratory failure.Cardiac involvement is not usually experienced	Classic Infantile Onset usually within first month of life. Non - classic infantile Pompe usually appears in the first year of life. Late onset presents in children or adults	Incidence: 1/201 000 Prevalence 1/146 000	Bailey (2008); Brady & Schiffman (2004); Deegan & Cox (2010); Tinkle & Leslie (2010); Van der beek, Hagemans, Van Der Ploeg, Reuser, & Van Doorn (2006)
The glycogen storage disorders	glycogen accumulates					

ERT works by replacing the missing enzyme with an artificial enzyme produced using recombinant DNA technology (AGDHA 2010b,c,d,e). The artificial enzyme has been modified to enable uptake by the lysosome and is supplied to the body through intravenous infusion. This intensive intervention holds much promise; however, is not a cure. ERT infusions are administered either weekly or fortnightly (Bailey, 2008; Clarke & Heppner, 2011), with sessions lasting from two to six hours depending on the particular enzyme and dose (Bailey, 2008). Treatment is currently life-long, and deteriorations are observed when infusions are regularly missed (Martins et al., 2009; Sifuentes, et al., 2007). Improvements in growth, cardiac function, lung capacity, strength and joint mobility have been described in association with the intervention (Bailey, 2008; Coman et al., 2008; Brady & Schiffmann, 2004; Martins et al., 2009; Meikle & Hopwood, 2003; Packman, Crosbie, Behnken, Eudy & Packman, 2010; Sifuentes et al., 2006; Van der Beek et al., 2006). Reductions in joint pain and in liver and spleen size have likewise been documented (Meunzer et al., 2004; Sifuentes et al., 2007)

One limitation is that ERT does not ameliorate all symptoms of a lysosomal storage disorder equally (Beck 2007). Fewer benefits are derived if the enzyme preparations are received later in the course of the disease (Beck 2007; Muenzer, 2004). Commercially available enzymes do not cross the blood brain barrier, so ERT cannot improve or prevent the progression of the neurological symptoms of MPS (Bailey, 2008; Brady & Schiffmann, 2004; Clarke & Heppner, 2011; Deegan & Cox, 2009; Muenzer, 2004). Likewise, for some patients delivery of enzyme may not improve skeletal joint stability (Wraith et al, 2008).

Allergic reactions have been identified as a negative outcome and potential side effect for patients (Beck, 2007, Wraith et al 2008). These can usually be managed by slowing the rate of infusion delivery or providing preventive medication (Beck, 2007).

Not all patients with MPS I, II, Pompe or Gaucher are eligible for ERT. Patients who are not, and hence their families, have their own unique experiences in relation to the effects of illness and prognosis. The perceptions of young people and families who are eligible for this treatment are thus likely to be different, as the groups are distinct. The purpose of the present study was to capture the experiences of the

group accessing ERT.

ERT is not currently available through the Pharmaceutical Benefits Scheme in Australia due to the rarity of the conditions, and significantly high costs of treatment, estimated between \$200 000 - \$300 000 US per patient per year (Bailey, 2008). Patients access enzyme therapy through the Life Saving Drugs Programme (LSDP), so specific eligibility and monitoring requirements must be met and not all patients qualify [Australian Government Department on Health and Ageing (AGDHA), 2010a,b,c,d,e; Coman et al., 2008]. Given the large expenditure on these conditions, it is important to obtain information on all aspects of treatment, including the psychosocial implications.

Whilst a significant body of literature exists pertaining to the medical benefits and limitations of ERT for lysosomal storage disorders, research exploring the psychosocial experiences of young people receiving ERT and their families and how this influences lifestyle is scarce. Adults in a Packman et al. (2010) study about living with Gaucher disease spoke of the impact regular ERT had on social lives and fear of the consequences of missing infusions. Previous research focusing on young people living with a chronic condition has looked at associated psychological stress on patients (Barlow & Ellard, 2006; Taylor, Franck, Dhawan, & Gibson, 2010), parents (Nærde, Tambs, Mathiesen, Dalgard, & Samuelsen, 2000) and siblings (Barlow & Ellard, 2006; O'Brien, Duffy & Nicholl, 2009; Sharpe & Rossiter, 2002). Young patients may feel a sense of isolation, experience difficulty making friends or face academic challenges due to absence from school (Barlow & Ellard, 2006; Taylor, Franck, Dhawan, & Gibson, 2010). Likewise, accessing treatments and managing symptoms such as pain, illness and fatigue interferes with other activities, potentially this impacts upon the whole family (Barlow & Ellard, 2006). Essentially these factors tie into health related quality of life (HRQoL), a multidimensional concept and an important issue for young people (McDougall, Horgan, Baldwin, Tucker & Frid, 2008; Spieth & Harris, 1996; Taylor, Gibson & Franck, 2008) with a lysosomal storage disorder and their families.

Levels of parental stress have been compared to the level of support available and the degree of their child's illness with stress worsening if support was limited or the child's difficulties seen as severe (Tadema & Vlaskamp, 2009; Waisbren, Jones, Read, Marsden, & Levy, 2004). Taedma and Vlaskamp

(2009) found parents who spent more time undertaking activities of daily living (e.g. feeding, dressing) and health related tasks for their child perceived a greater amount of burden than other parents did. Similarly, Waisbren et al. (2004) discovered that parents' who felt less successful in meeting their children's needs and less satisfied with their own support networks experienced more stress; children's own adaptive functioning skills were also significant in that the less well developed these were, the greater the stress experienced by parents. Likewise, accessing treatments and managing symptoms such as pain, illness and fatigue not only cause concerns, but also interfere with other activities, potentially impacting the whole family (Barlow & Ellard, 2006). Essentially these factors tie into health related quality of life (HRQoL), a multidimensional concept and an important issue for young people (Mc Dougall, Horgan, Baldwin, Tucker & Frid, 2008; Spieth & Harris, 1996; Taylor, Gibson & Franck, 2008) with a lysosomal storage disorder and their families.

Often when research into chronic conditions focuses on young people, it is the parents or health professionals who participate in the studies, leaving young people's opinions to be conveyed by proxy; however, young people have opinions and it is important they have their thoughts heard. To understand the impact that living with a metabolic condition and receiving ERT exerts on health related quality of life, it is important to give young people a voice (Coyne, 2005; Drew, Duncan & Sawyer, 2010; Taylor, Frank, Dhawan & Gibson, 2010; Mack, Giarelli & Bernhardt, 2009).

Issues of communication have also been investigated, with studies indicating that families desire good communication with their health professionals (Dickinson, Smythe & Spence, 2006; Reeves, Timmon & Dampier, 2006; Zierhut & Bartels, 2012). Likewise, young people's experiences with health care professionals influence their attitudes towards their condition, ability to trust medical staff, and adherence to treatment (Taylor et al. 2010). Communication with other family members is similarly an important consideration, especially for families touched by a lysosomal storage disorder (Hartley, Greenberg & Mhanni, 2011) and for the professionals supporting them.

Purpose of the Study

This study sought to explore how living with a lysosomal storage disorder and receiving ERT impacts the quality of life of young patients and their families. Given the nature of the conditions and intensity of

treatment, there are potential implications for other family members. Drawing on the biopsychosocial model, this study focused on a cohort of young people in Melbourne who receive ERT to treat a lysosomal storage disorder to look at this influence. Health related quality of life (HRQoL) acknowledges that physical, psychological, social and environmental aspects interact to influence an individual's well-being. Biopsychosocial models reflect this interaction (Mc Dougall, et al., 2008; Taylor et al. 2010; WHO, 2002). Figure 1 illustrates this relationship as it applies to living with a lysosomal storage disorder and receiving ERT. The aim in using the biopsychosocial model for this study was to capture the perceptions of young people with MPSI, MPSII, Pompe or Gaucher diseases who receive ERT and their families; exploring the influence, in regard to:

- The impact of intensive and regular hospital appointments.
- The psychosocial implications associated with the physical benefits and limitations of ERT, the clinical features, diagnosis, prognosis and management.
- Young people's and families' understanding of their condition and treatment.
- Impact of the condition and access to treatment on decision making and thoughts about the future.
- Implications for clinical practice.

METHODS

Participants

Participants were selected through purposive criterion sampling and represented three groups, patients receiving ERT to treat a lysosomal storage disorder, siblings and parents. An eligible cohort was identified by members of the metabolic team at a major pediatric tertiary hospital in Melbourne. At the time of the study, eight patients with a lysosomal storage disorder who received ERT were being managed by the metabolic department of the hospital. Eligibility criteria for patient participants included having a diagnosis of a lysosomal storage disorder and receiving ERT to treat it, or having a child or sibling who was receiving ERT to treat a lysosomal storage disorder. No limit was placed on the length of time for which a patient had been receiving ERT. The definition of "young person" was thought of as individuals aged less than 25 years. In order to participate in an interview, the interviewee needed to be aged 10 years or older. Piaget's theory of cognitive development suggests children at 10 years old have

almost completed the “concrete operational” stage of thinking and are entering the “formal operational” stage (Huffman, Vernoy & Vernoy, 1998; Sternberg, 2000) in which their thoughts show increased rationality and maturity (Mack et al., 2009). Therefore, the authors felt that this was a suitable age in which to speak to young people in an attempt to elucidate their perspectives on living with a lysosomal storage disorder and receiving ERT. The restriction placed on age was in regard to participation in an interview only. This meant that any parent from the identified cohort was eligible to participate, even if they cared for children aged less than 10 years (assuming their child received ERT). The views of parents with younger children were recognised as being equally as valuable and important to articulate as those with older children.

A total of nine parents, four patients and three siblings participated. The exclusion criteria included patients with a lysosomal storage disorder not receiving ERT and patients with a known intellectual impairment were not able to participate. Children were required to be well enough to engage in a lengthy conversation at the time of the interview, in order to participate optimally and not find the interview experience aversive or uncomfortable.

Instrumentation and Procedures

A series of semi-structured interviews were conducted with participants (see Appendix I, interview guide). Interviews were conducted by the first author. All interviews were recorded digitally and transcribed verbatim. Whilst the interviews were client led and flowed like a discussion, the biopsychosocial model assisted when developing the interview guide, which covered the following:

- physical and medical impact of the condition and physiological benefits and limitations of ERT (biological)
- psychological impact of living with a chronic condition (or such a condition in the family) and receiving intensive treatment for it, and
- issues associated with communication and relationships (social)

It was felt semi-structured interviews would better capture participant perceptions of living with a

lysosomal storage disorder and receiving ERT than standardized QoL scales. Standardised scales have their utility especially when focussing on a large number of participants or looking at individuals to design specific treatment goals; however, they are often prescriptive. Semi structured interviews are conducted in a more conversational style allowing more opportunity for interviewees to discuss issues they perceive as salient to individuals and families. Interviews covered the areas of experiences of living with a lysosomal storage disorder (or living with a lysosomal storage disorder in the family), experiences receiving treatment and life in general as they applied to parents, patients and siblings (see Appendix I for examples of questions).

To participate optimally in research, young people need to feel engaged and have fun (Barker & Weller, 2003). Qualitative interviewing, whilst allowing stories to be told is a very adult form of conversation. Therefore, to build rapport and facilitate discussions, in a non-threatening manner the “child-centered research techniques” of photo elicitation (Drew et al., 2010; Epstein, Stevens, McKeever & Baruchel, 2006) and “draw and tell” (Barker & Weller, 2003; Driessnack, 2006; Hortsman, Aldiss, Richardson, & Gibson, 2008) were employed. Similarly, as Epstein et al. (2006) suggests, ideas evoked by photos can be explored in the process of the interview. For the purposes of this study, photos were shown depicting “everyday” images likely to resonate with young people such as an iPod, computer games, classroom, football, pets, etc. Photos illustrating “medical treatment” such as an IV medicine bag, the hospital building, etc., were also shown (see Appendix III for examples). During the early phases of the interview, young people were asked to choose two (or more) photos they found “interesting”; they were able to discuss any topic or memory sparked by that photo. Once the “everyday” photos had been discussed, they were asked to choose a photo representing life with their condition or going to the hospital (if not picked initially).

The “draw or write” activity provided a further opportunity to discuss the issues the young patients and siblings felt were important. The young people were asked to draw anything that symbolised receiving ERT or living with a lysosomal storage disorder to them. Alternatively, if they preferred, they were also able to write down any words or phrases that they thought represented this phenomenon (see

Appendix III, for examples). Whilst most chose to write lists or asked the first author to scribe, one boy drew his IV pole, talking about various issues he felt were important whilst he drew. It was thought the change in task, particularly making the activity more creative would assist in maintaining young people's engagement, stimulate new thoughts, generate additional ideas and reflect those that had already been revealed.

Child centered techniques were not used with adult participants (those aged 20 years or older) as it was felt they would manage well with an interview, being more experienced with this type or intensity of conversation. Therefore, the technique was used with six participants in total, four patients and two of the three siblings.

Data Analysis

To ensure rigorous analysis, the steps for conducting thematic analysis as outlined by Braun and Clarke (2006) were followed. The 15 interview transcripts were read multiple times, so that the authors were familiar with the concepts being conveyed, concurrently making notes about their impressions. The first three authors were responsible for reading and coding the transcripts. The note making or "memoing" (Braun & Clarke, 2006; Starks & Brown Trinidad, 2007) was an ongoing process. One transcript was analysed at a time. Codes were generated and assigned to salient aspects of the interviews; it was acknowledged that some portions of conversation covered multiple codes. In coding each of these transcripts common patterns were sought, additional impressions recorded and thoughts discussed. Similar codes were categorised into clusters and then tables and thematic mind maps (see appendix II) were generated in order to see these individual concepts laid out in groups together and observe any links between each. This step assisted in further identifying and consolidating themes. Emerging themes were checked against the coded aspects of the transcripts, these were then refined and finally names were given to each.

The biopsychosocial model assisted with interpretation and analysis of emerging concepts, in which themes were categorized according to whether they better encompassed a biological, psychological

or social issue. Biological issues were deemed to be those relating to the physiological symptoms of the condition, the physical actions involved in receiving ERT and associated therapeutic benefits and restrictions. The psychological theme incorporated perceptions about daily living and adjusting to life with the condition and ERT regime, the emotional impact, participants thought processes, decision-making and coping styles. Themes categorised under social issues focussed on the influence of the condition and treatment on interactions with others, communication and relationships. The Nvivo 9 software package assisted with data storage and management.

Figure 1: Health related quality of life in relation to ERT and lysosomal storage disorders (adapted from Mc Dougall et al., 2008; Taylor et al., 2010; WHO, 2002)

Explanation: The middle circle represents Health Related Quality of Life. The outer circles representing the different areas which impact upon this individually, i.e. physical symptoms of the condition, the benefits and limitations of treatment (what it can do, what it does not do and challenges associated with this) and the psychological and social impact (here one circle represent two different domains). The wider, shorter arrows indicate that each of these areas have a direct influence on HQoL. The longer filled arrows represent the reciprocity of domains that have an impact on each other, for example, increased energy is a benefit of treatment, leading to feelings of well being and the ability to keep up with peers in sports. The long dotted arrow represents relationships that are not reciprocal, for example, maintaining good social relationships with peers or a positive attitude may not influence the actual features of the condition, however these can have a definite impact on relationships, and psychological well being. HRQoL is also influenced by the environment in which one functions, their own personality, whether it is they who are affected or a family member, their own experiences, age and developmental level, all of these can change with time, they are represented by the blank space and terms around the edge of the diagram.

RESULTS

PARTICIPANT CHARACTERISTICS

Eight families were invited into this study; seven families participated. From these seven families, fifteen interviews were conducted, transcribed and analyzed for themes. Nine parents, four ERT patients, and three siblings were interviewed. Eight parent interviews were conducted, as one couple wished to be interviewed together. All siblings were invited to participate if they were aged over 10 years, but due to feasibility and time constraints not all were interviewed (Table 2 shows participant characteristics). The eighth family had no representatives due to availability and scheduling difficulties rather than the desire not to participate. Of the four non- participating ERT patients, one did not meet the minimum age requirements so therefore was ineligible for an interview; three did not wish to be interviewed.

INTERVIEWS

Seven interviews were conducted in the hospital's ambulatory care facility whilst patients received infusions. These took place in a common area, separate from other people to maintain privacy. The option of a private room was provided, however only two were conducted in private rooms, as most participants preferred the common space. Six of the 11 non-patient interviews were conducted remotely through phone calls, videoconferencing or *Skype*. Interviews ranged from approximately 15 minutes to an hour in length. The median length of interviews was 20 minutes with siblings, 30 minutes with patients, and 45 minutes with parents.

Table II: Participant Characteristics

	Pseudonym and gender	Participant group	Disorder	Patient's or sibling's age
1	Max (M)	ERT patient	MPS II	12 years
2	Ben (M)	ERT Patient	MPS II	10 years
3	Jamie (M)	ERT patient	MPS II	11 years
4	Greg (M)	ERT Patient	MPS I	15 years
5	Belinda (F)	Sibling, brother has ERT	MPS I	20 years
6	Cameron (M)	Sibling brother has ERT	MPS II	14 years
7	Will (M)	Sibling brother has ERT	MPS II	10 years
8	Michael (M)	Parent, son has ERT	MPS II	Parent of primary school age child
9	Jessica (F)	Parent son has ERT	MPSII	Parent of primary school age child
10	Trisha (F)	Parent, son has ERT	MPS II	Parent of primary school age child
11	Wendy (F)	Parent, son has ERT	MPS II	Parent of primary school age child
14	Sandra (F)	Parent ,son has ERT	MPS II	Parent of teenager
13	Kristy (F)	Parent ,son has ERT	MP I	Parent of teenager
12	Rob (M) and Sally (F)	Parents, daughter has ERT	Pompe	Parent of primary school age child
15	Steve (M)	Parent, son has ERT	Gaucher	Parent of teenager

Parent Participants: *n*= 9, Patient Participants: *n*= 4, Sibling Participants: *n*= 3

INFLUENCES OF LIVING WITH A LYSOSOMAL STORAGE DISORDER AND RECEIVING ERT ON HRQOL

The themes that emerged from the interviews are portrayed within the domains of the biopsychosocial model. This model is dynamic and reciprocal in nature, so consequently there is some overlap as several themes cross over domains as illustrated in Fig 5. Table III provides a summary of these themes. Themes categorized within the biological domain relate to the physiological symptoms of the condition and the physical actions involved in receiving ERT, its therapeutic benefits and restrictions. The psychological domain explores people’s perceptions about daily living with the condition, adjusting to the ERT regime, the emotional impact, thought processes, decision-making and coping styles. The social domain looks at the influence of the condition and treatment on interactions with others addressing the themes of communication and relationships.

Figure 2: Biopsychosocial model for receiving ERT and living with a lysosomal storage disorder

These themes are introduced here by mini verbatim quotes, to capture the participants' own language.

Biological impact, experiences of the condition and treatment:

***“Live it to the max”*: Positive outcomes from ERT**

In speaking about the outcomes achieved from ERT, a direct and ameliorative affect on physical health was described, particularly with respect to energy. Participants articulated how physical improvements promoted psychosocial well being:

When I didn't have the enzyme I was sort of, I was sometimes sad 'cause I couldn't keep up and then when I do have the enzyme it makes it happy, like it makes me outgoing, like doing all these things, makes me do more active, it makes me excited. (Ben, 10 yrs, MPSII).

“I've got a life and I'm going to live it, I'm gonna live it to the max” that's how he says it, that's how he talks. (Sandra, mother of teenager with MPSII).

***“Sometimes he cracks it”*: The challenges, restrictions and limitations of accessing ERT**

Participants explained that they were able to accept the intensity of regular infusions and the restrictions the LSD placed on their lives, although admitted to finding these challenging. As noted by parents, time

spent in hospital appointments and occasional negative side effects cause young people to feel ‘fed up’. A sense of “missing out” on school, employment, travel, and recreational activities due to treatment as well as LSD symptoms was described:

He is not allowed to play footy because of tackling and the potential instability in his neck which really devastated him, so I had to be quite graphic and explain why (Jessica, son has MPSII).

Does having the [drug named] limit us in terms of going overseas; could we still access the drug and holidays? We have some concerns with family holidays we went to [place] and made it a 10-day holiday because he had to be back in time for the treatment. But if we wanted to go to somewhere like England or Canada, then how do we do that, with our children?(Wendy, mother, son has MPSII)

I’ve kept part time because I’ve had to keep part time; I could never hold down a full time job if I wanted to and keep up with all the appointments. (Sandra, mother of teenager with MPSII).

“That would be just like heaven”: Flexibility and alternatives in treatment delivery

At the time of the study, for these patients ERT was delivered intravenously at the children’s hospital during regular business hours. Receiving infusions after school, on weekends or at home was suggested as a potential solution to make accessing treatment more straightforward. Several participants were aware of the availability of home-based infusions overseas. Some expressed interest in joining a clinical trial investigating home infusions if any were to be established in Melbourne; others appeared apprehensive about the home-model:

[Dr] mentioned that they could just come to your house, or is that too good to be true? because that would just be like heaven (Kristy, mother of teenager with MPSI).

Overseas they do home infusions, I don't know how I feel about that ... I quite like separating the medical from the home (Jessica, mother, son has MPSII)

Psychological impact, coping mechanisms and decision-making

No Regrets: Decisions to commence ERT and attitudes towards treatment

Faith in the efficacy of ERT for fighting the LSD and improving health appeared to be the motivation to commence therapy:

Before the enzyme, what was happening was [son] was getting worse... there'd be this progression, this deterioration all the time ...so we were sort of really stuck, we didn't really have anything to fight the disease with then (Jessica, son has MPSII).

Participants felt grateful to access ERT and emphasized how they would not change their decision. Even parents whose children experienced a comparatively milder form of the condition, and felt treatment regimes could be less rigid expressed the idea of non-regret:

For him ...having started on treatment, the difference it's made has been fantastic and we do not for a moment regret that decision (Trisha, mother of son with MPSII).

Some acknowledged concerns they would have if treatment were to become unavailable

My mum just told me the government were paying for it and it would get worse if he stopped taking the medication and if the government stopped funding it, it would be kind of disastrous. (Will, 10yrs brother)

“It doesn't affect me that much”: Minimizing the impact of the condition and treatment

Patients seemed to minimize the affects their LSD and demands of treatment placed on their lives. Siblings described feeling the impact was of less significance because they were not the one affected. Some participants recalled traumatic events, yet many continue to focus on positives:

We've had so many obstacles being thrown at us. We've had people saying you can't do this or you better not to do this. But we've been proactive so we can do things, we have skills and abilities and we want to pass those onto our children. (Wendy, son has MPSII).

One mother, however spoke about the severity of her daughter's Pompe symptoms and how difficult living with the condition could be:

It's ongoing, you don't get much time to sit down as you do all the feeds all the time and so forth like that, and the medications. (Sally, mother, daughter has Pompe).

“Cross that bridge when you come to it”: Managing uncertainty and future thinking

You do worry about little things, like will it get worse later, but cross that bridge when you come to it, otherwise, you'll shoot yourself worrying. (Michael, son has MPSII).

Naturally, parents had concerns for their children's future; however, some appeared to manage these more successfully than others:

I get very stressed easily... I do worry about his future ... and I am concerned, but there is no sense worrying about things you can't control, but I am a worrier. (Kristy, son has MPS1).

Whilst some young people discussed the future, most were engaged in the present and did not focus on the potential impact of ERT on future endeavors. Parents believed in encouraging confidence and independence as they felt these to be important attributes their children could employ later in life. They presented an awareness that their children might eventually need to manage the LSD themselves; this was linked to fostering a working knowledge of the condition and communicating with professionals:

We used to come up and take [son] with us whenever we talked to the doctors, and ask “Is there anything you want to say?” and try to give him some of that power and control back, because it is his disease and his problem. It's important that people don't forget him in the whole process, so kept communication lines as open as possible. (Wendy, son has MPS II).

“What happens happens”: Adjustment and maintaining normality

I actually don't mind coming here. I would rather not have it or why it happens, but what happens happens, so this is what happened (Jamie, 11, MPSII).

Many participants demonstrated acceptance. Most families appeared to have ERT sessions well established in their weekly routine, however reported on challenges associated with this:

We've worked very hard, at the start he was really negative, it was really different, "I don't want to be here"...we've worked very very hard to just get it as part of our routine. (Trisha, mother, son has MPSII).

Social impact, communication and relationships:

“Just hanging out with mates”: Peer and sibling relationships

The importance of friendship was described by young people in the context of everyday activities. During the writing task “friends” appeared on lists of important aspects of life. The comfort levels for disclosing information to peers differed amongst young participants. Some were open, whereas others were cautious:

Talking and seeing my friends usually helps... they know about it, they have been a great support. (Belinda, sister of teenager with MPSI).

Well at this school they know I go here, but they don't know why. I am trying to keep it a secret My best friend knows. (Jamie, 11, MPS II).

Generally unaffected siblings appeared empathic, demonstrating compassion. Some parents expressed concerns regarding how children without the LSD might feel left out, reporting on issues that had risen in the past but overall felt adept at handling the feelings of unaffected siblings in regard to being ‘left out’. Siblings did not feel themselves “being left out” was hugely problematic or occurring too often.

“We are really open”: Maintaining communication with family members and professionals

Most parents addressed the importance of being open with children and family members. Some felt a responsibility to tell their own siblings about the condition; they touched on issues associated with genetic testing, IVF and pre natal diagnosis, expressing how sensitive such topics can be.

I have these two sisters, and they'd all at that stage had baby boys, and there was a sense of responsibility I guess as we then had to tell them. (Jessica, mother, son has MPSI)

We put them (first degree relatives) in touch with the genetic counselors here and discussed what we knew about the condition ... and made it clear, that if at any time they(relatives) found out, about any decisions they were making, it was not our place and I did not want to know (Trisha whose son has MPSII, commenting on the sensitive issue of other people's choices when it comes to reproductive options and decision making regarding conception and actions after prenatal diagnosis).

The way professionals relate to patients, especially whilst receiving infusions seemed pivotal in shaping experiences. Most of the examples provided were positive, although stressful events were recalled vividly.

The doctor there was quite insistent on doing procedures in a certain way all of the time ...[son] found that very stressful because he lost all of his control and all of his power. (Mother, son with MPSII)

“Anything to help”: Parental involvement, advocacy and altruism

Parents described their role in helping their children involved some degree of advocacy. They remarked on how difficult this could be. Some participants identified speaking to similarly affected families as beneficial, particularly at the beginning of their journey with the condition or treatment. Some parents were even involved in formal lobbying for Elaprase® to become available through the LSDP:

Well it was scary, and I didn't really know what I was doing, but I thought I am not going to make

it any worse ... so we did all the letter writing and those things, but I think what really worked was I lobbied my local member of parliament. (Jessica, mother, son with MPSI).

Table III. Themes Emerging from Interviews

Domain	Category	Themes
Biological Impact	Experiences of the condition and treatment	<ul style="list-style-type: none">• Positive outcomes of ERT• Challenges, restrictions, limitations of the conditions and ERT• Flexibility in treatment delivery• Understanding of the condition and its treatment
Psychological Impact	Coping mechanisms and decision making	<ul style="list-style-type: none">• Attitudes towards ERT• Minimising the impact of treatment• Managing uncertainty• Adjustment, acceptance and maintaining normality
Social Impact	Communication and relationships	<ul style="list-style-type: none">• Friendships and peer relationships• Sibling relationships• Maintaining open channels of communication with family and professionals• Altruism, advocacy and parental involvement

Bold font denotes dominant themes

DISCUSSION

Biological impact, experiences of the condition and treatment

Metabolic conditions require lifelong management (Hartley et al., 2011) and ERT is associated with multiple positive outcomes (Bailey, 2008; Brady & Schiffmann, 2004; Packman et al., 2010). The present cohort possessed an optimistic attitude about ERT and expressed excitement. The participants described the improvements in health they had observed in their selves, their children or their siblings and how these improvements resulted in recognizable benefits to HRQoL. Parents conveyed relief that disease progression could be slowed and ameliorative affects achieved. The sentiments conveyed by these participants reflect those documented by Sifuentes et al. (2007), who described increased energy and a desire to enjoy life in their follow up of patients receiving Laronidase® for MPSI. Unfortunately, ERT does not alleviate all of the associated difficulties as learnt from previous studies (Beck, 2007; Brady & Schiffmann, 2004). Parents in the current cohort explained how some features could not be “fixed” and

the impact this had on their children. As described by the participants in this current study, alongside the positives, come challenges of which professionals can be aware. Great time commitments are required resulting in absences from school or employment. This can ultimately influence lifestyle choices. Most participants appeared to adjust to the need for ERT in their life, however they still felt the pressure of regular infusions and attending specialist appointments. Patients and families of this present study expressed how they access treatment at expense of other pursuits such as education, employment, recreation and travel. Such sacrifices are a source of frustration and disappointment, yet the 'trade-off' is acceptable as treatment outcomes are far superior to rewards gained from other activities.

Education was viewed as a high priority by participants. Parents felt the demands of a primary school classroom could be met despite the time-constraints involved in receiving ERT, although they raised concerns in relation to secondary school. The need to take action to ensure their children were not disadvantaged academically was addressed. Whilst some parents made plans in this respect, they admitted to not always being certain about what to do. Most discussed the importance of communicating their needs to both their child's school and hospital staff, in the hope that individual needs could be accommodated. Health professionals working on metabolic teams may be faced with discussing educational issues; they can assist families by listening to concerns, making referrals or liaising with teachers to provide disease information. Such support might be especially important when commencing ERT or during transition times.

Participants commented that they would like more flexibility in how they access ERT; they believed having options to attend after school or on weekends would be helpful. Currently, this is only possible if patients go to a hospital other than RCH for their infusion. The advent of home-based infusions overseas had already sparked interest amongst participants; several thought accessing ERT at home, as can be done in the UK (Hughes, Milligan & Mehta, 2007) and America (Burton et al., 2009), may partly reduce the disruption they felt. Home infusions are not currently offered in Victoria, and

whilst most parents demonstrated a readiness to try the home-model, some reported their children felt apprehensive, and others stated they preferred separating home life from medical treatment.

Psychological impact, decision-making and coping mechanisms

Naturally, parents want to ensure an optimal level of health for their children. This desire seems to have driven decisions to commence treatment. In gaining insight into the influence of ERT on HRQoL, it is essential to consider families' experiences with their treatment journey. For some patients, ERT was available at the time of diagnosis or shortly afterwards. For others, the wait was longer and greatly anticipated. Some participants felt that as their condition was mild they were probably "fine" before ERT, however the importance of commencing treatment early, before the onset of irreversible effects is now known (Sifuentes et al., 2007; Wilcox, 2004). Some parents seemed more anxious about the future than others did, a difference that may be attributable to the severity of their child's condition or their own coping styles. Parents described how children might need to manage the condition themselves at some point; such concerns are commonly expressed by parents of children with genetic disorders (Giarelli, Bernhardt, Mac, & Pyeritz, 2008). Genetic counselors can have a role in ongoing care, supporting patients and families at pivotal times during their lives (Hartley et al. 2011). Young people were generally optimistic about the future, although they appeared more focused on the "here and now"; few revealed thinking about how ERT or their LSD might influence plans.

Common coping mechanisms were described as participants discussed ways of managing the impact of their conditions and treatment. Participants attempted to normalize their situations and set up routines. Many focused on "positives" such as personal strengths, success of ERT and enjoyable aspects of their lives. The parents of the young person with Pompe however, spoke in more detail about the challenges their family faced, the impact on their daily activities, as well as their own social functioning. When considering the findings from this study, it is important to acknowledge only one Pompe family participated, so their views may not be the same as those of other families affected by Pompe or another lysosomal storage disorder. The findings can be viewed as a spectrum of attitudes and experiences that

are present for patients and families accessing ERT for a lysosomal storage disorder.

Taking a “one day at a time” approach or “*delaying worrying*” (Stewart & Mischel, 2000) was presented as a way to manage uncertainty. Uncertainty is related to psychological stress (Stewart & Mischel, 2000) and particularly important as ERT is not a cure. Zierut and Bartels (2012) report on information gathering and fostering open channels of communication with health professionals as other strategies. Most parents in our study similarly reflected on these techniques. Whilst many appeared to employ beneficial or adaptive coping mechanisms, in a clinical setting it would be important to recognize when strategies are maladaptive. Such coping strategies fail to decrease or ameliorate distressful situations. For example, denial behaviors may influence compliance with medical recommendations or lead to distancing oneself from those who could offer support.

Social impact, communication and relationships

Several parents addressed the importance of developing working knowledge of the disorder and its treatment. They share information and encourage their children to be actively involved in medical appointments. As knowledge facilitates a sense of control (Coyne, 2006) this level of communication positively influences young people’s coping and adjustment (Metcalf, Plumridge, Coad, Shanks & Gill, 2011; Taylor et al., 2010). Most parents felt a responsibility to inform family members of the LSD diagnosis, recognizing the implications for health and reproductive choice. Some parents spoke about genetic testing, termination and PGD. Sensitive topics need to be understood in relation to this unique population. It is useful to know how families would like to communicate information and how such discussions can be facilitated. Genetic counselors are well placed to support those wishing to communicate difficult or complex information (Hartley, et al., 2011; Levy-Lahad & Zimran, 1997; Meunzer, 2004; Mickle & Hopwood, 2003; Wilcox, 2004).

Young people described mostly good relationships with hospital staff, although some participants disclosed negative experiences. Infusion therapy is a significant part of the weekly routine so unpleasant

experiences could be detrimental to HRQoL. Mack et al. (2009) emphasize that listening to young patients and respecting their need for information is essential. Adverse experiences may cause young people to resent treatment or mistrust staff.

Friendships play an essential role in quality of life (Spieth & Harris, 1996), providing support and a sense of normality, particularly for patients who see themselves as different (Taylor et al., 2008). The young people in our study indicated how important friendships were to them. Highlighting positive aspects of an individual's life can assist them to cope with adversity and provide a sense of empowerment (Kessler, 1997). It is especially important to recognize strengths during adolescence, a sensitive time in which complex developmental tasks are being met (Taylor et al, 2008) and to which clinician's can take a sensitive approach (Mack et al, 2009).

Some parents in the current cohort spoke altruistically about their desire to help others and described talking to other families as being beneficial. Whilst each family has a different journey, their experiences are likely to have similarities. Negotiating healthcare systems and coping with diagnoses, prognoses and treatment can be difficult. Families are able to support one another.

CLINICAL IMPLICATIONS

“Genetic Counseling has emerged to respond to the individual seeking genetic information and has taken up the challenge of how the knowledge of the genetic contribution of a disease is shared with individuals and families” (Evans, 2006 p.xvi). The themes identified through this study emphasise the importance of understanding genetic information and the ways of successfully communicating this information to each individual and family.

Genetic counselors through their training are well placed to understand the complex genetics associated with chronic conditions and to effectively communicate this information to each parent and young person; taking an individualised approach to account for their clients' particular needs. ERT is an

intervention that may affect the current lifestyle of patients and families, influencing the way they experience the condition. Genetic counselors discuss the potential impact of treatment and work with families and individuals to consider their options and facilitate their decision making about the process. Intrinsic to the role of a genetic counselor is their ability to support clients to understand pertinent information and to make informed decisions. These are often complex tasks to achieve; requiring information provision to be balanced with empathy and a non-directive, compassionate approach. By reflecting upon the treatment experiences of clients with whom they meet and learning about the activities involved in accessing particular treatments, genetic counselors are uniquely positioned to act as these supports.

For participants of this study, ERT appears to be having an overall positive influence on HRQoL. Most participants seemed well adjusted and adept at managing stressors, although many described stressful or traumatic experiences. Working with such a population requires making the best effort to recognize psychological distress or sources of stressors and assist where possible. Many participants demonstrated resilience, bravery, and compassion. Identifying and working with strengths is likewise valuable, as patients and families will progress through life stages experiencing success and adversity.

FUTURE RESEARCH

As participants described a desire for more flexibility with service delivery, one suggestion for future research is to investigate attitudes to home infusions in more depth. This could involve sampling a larger cohort, including adults and other conditions for which ERT is available (e.g. Fabry disease). Similarly, an expansion of this study to involve a greater number of participants, or compare the perceptions of adult patients to those of the young patients might yield interesting themes that can be applied in clinical practice.

Future studies could examine how to educate health professionals in the wider community about addressing rare genetic conditions. Likewise, looking into how best to provide information to newly

diagnosed families would be worthwhile. Exploring approaches for working with young people affected by inborn errors of metabolism who want to communicate information to friends, teachers, employers or partners would be equally valuable.

STUDY LIMITATIONS

Lysosomal storage diseases are rare conditions. At the time of the study, only eight patients were being managed through the metabolic department at the hospital who were actually receiving ERT for LSD. This resulted in only eight families being eligible to participate and thus reduced the number of eligible participants for the study. All but one of the eight families were represented; the family that was unrepresented, accepted the invitation to participate but due to difficulties with scheduling times was never able to attend an interview. The views of the individuals from this family may have differed and this would have been reflected in the results. Similarly, the small numbers meant that MPS II was over-represented in this cohort. These are heterogeneous conditions. Whilst patients and families affected by MPS I, Pompe, Gaucher and other lysosomal storage disorders have similar experiences associated with living with their condition and receiving ERT, there are also likely to be other salient issues which may not have emerged as themes from this data.

One aim of this study was to provide a voice to young people affected with a lysosomal storage disorder, however a larger number of parents participated. Due the over-representation of parents in the cohort, compared to young patients and their siblings; it is possible parent voices were more dominant. This may have influenced the themes that emerged.

Most participants appeared to be coping well and had a generally optimistic outlook. This may not be the case for all patients accessing ERT for a lysosomal storage disorder. The young people who participated appeared well adjusted and confident. For patients who did not participate, the parents described similar characteristics. It is difficult to know with certainty whether these are the real feelings of those young people, or if the reasons for not participating run deeper than not wishing to engage in an interview. Most of the young people in this study were demonstrating physical improvements and it seems likely this would influence their own and their family's perspective.

Essentially three groups of participants were included in the study, parents, siblings and patients. This effectively meant the numbers representing each group was small, and this presents a limitation. Undoubtedly, participants' experiences will be different depending on whether they live with the condition and receive treatment, care for a child who does so or have an affected sibling. However, given the clinical and genetic nature of the conditions and intensity of treatment, there are potential implications for other family members. Reflecting their thoughts was also seen as important. The generalisations need to be viewed in light of the fact a small number of voices articulated their opinions. Despite this the concepts conveyed have been addressed in previous literature, and whilst they may be unique to this small cohort, such concepts have been identified in relation to lysosomal storage disorders and other chronic genetic conditions requiring intensive treatment (Barlow and Ellard 2006; Taylor et al, 2010).

The population, from which this sample was drawn, is small. Despite the confidentiality of the study, it is possible that participants know and talk to each other. Likewise, even though participants were reminded, and the interviewer ensured they understood that their access to treatment would not be affected by their choice to participate or decline, it is possible some felt an obligation above that of natural altruism; particularly given the gratitude and appreciation most feel towards accessing ERT. Most of the interviews were conducted in ambulatory care, and this may have caused participants to be more guarded in the information they shared, particularly young patients, whose nurses needed to check their status regularly.

CONCLUSIONS

Improvements in physical health associated with ERT result in increased psychosocial well being, as young people feel more energetic and confident. Although time spent in hospital is taxing and participants would like changes to the service delivery model, intervention is seen as essential and prioritized. Patients and families experience stress, although they have developed ways of adjusting to ERT. Parents appreciate good communication, they try to impart this belief to their children and link

possessing a good working knowledge of the disorder and its treatment to fostering independence. As lysosomal storage disorders are genetic, families feel a responsibility to inform close relatives, so that they may investigate options for genetic counseling or testing. Participants also commented on the way the LSD and access to ERT had influenced certain life decisions. Some worried about the future, whereas others focused on the “here and now.”

Understanding the benefits and challenges intensive treatments present and acknowledging past experiences and coping styles is essential when working with individuals with chronic conditions. These findings provide insights for supporting patients and families and tailoring the approaches taken to managing their individual medical and psychosocial needs.

Ethics Approval

Approval to conduct semi-structured interviews was granted by the Royal Children’s Hospital (RCH)’s Human Research Ethics Committee. In accordance with National Health and Medical Research Council guidelines, parents provided consent on behalf of children aged less than 18 years. Young people were required to demonstrate a suitable level of maturity and capacity to assent.

DISCLOSURE OF INTEREST

There is no conflict of interest to disclose.

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