Achalasia: outcome in children

Running title: childhood achalasia

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ABSTRACT

Background: Oesophageal achalasia is well-recognized but relatively rare in children, occasionally appearing as the "triple A" syndrome (with adrenal insufficiency and alacrima). Treatment modalities, as in adult practice, are not curative, often needing further interventions and spurring the search for better management. The outcome for syndromic variants is unknown. We sought to define the efficacy of treatments for children with achalasia with and without triple A syndrome.

Methods: We conducted a retrospective analysis of presentation and outcomes for 42 children with achalasia presenting over 3 decades to a major paediatric referral centre. Long term impact of the diagnosis was assessed by questionnaire.

Results : We identified 42 children including 6 with triple A syndrome. The median overall age at diagnosis was 10.8 years and median follow-up 1593 days. Initial Heller myotomy in 17 required further interventions in 11 (65%), while initial treatment with botulinum toxin (n=20) was ultimately followed by myotomy in 17 (85%). Ten out of 35 patients who underwent myotomy required a repeat myotomy (29%). Patients with triple A syndrome developed symptoms earlier, but had delayed diagnosis, were more underweight at diagnosis and at last follow up. Questionnaire results suggested a significant long term deleterious impact on the quality of life of children and their families.

Conclusion: Many children with achalasia relapse after initial treatment, undergoing multiple, different procedures, despite which symptoms persist and impact on quality of life. Symptoms develop earlier in patients with triple A syndrome, but the diagnosis is delayed and this has substantial nutritional impact.

(250 WORDS)

KEY WORDS: botulinum toxin, myotomy, complications, intervention, nutrition

INTRODUCTION

Achalasia is a rare condition in children, with an estimated annual incidence of approximately 0.1 case per 100,000 children.(1) Associations exist with trisomy 21(2) and a syndromic form (triple A syndrome - **a**chalasia, **a**lacrima, and **a**drenal insufficiency).(3) Adults and older children often present with progressive dysphagia, regurgitation of poorly digested food, weight loss and chest pain(4) while vomiting, anorexia and chronic cough are said to be more common presenting features in children under five years of age.(5)

Treatment options at all ages aim to eliminate symptoms by relieving the obstruction provided by the non-relaxing lower oesophageal sphincter, none of which provides a complete cure.(4) Surgical intervention in the form of myotomy has been the traditional approach via either a laparotomy or thoracotomy,(6) or more recently using laparoscopy or

thoracoscopy(7) or a per oral endoscopic approach.(8, 9) Myotomy is often compared against pneumatic balloon dilatation.(10-13) Botulinum toxin has been used successfully in selected patients, given by an endoscopically directed injection into the oesophageal muscle around the lower oesophageal sphincter.(14-16) Pneumatic balloon dilatation and botulinum toxin injection have been proposed to be more effective, with fewer complications and less costly, but most adult studies still rank myotomy as the gold standard, reserving other treatments for selected cases or treatment failure.(9, 15) High resolution manometry has clarified the wide clinical spectrum of achalasia(17) with differing treatment approaches more likely to be effective in some subtypes, and some patients never proceeding to any therapeutic intervention at all.(17, 18) The relative efficacy of myotomy and pneumatic dilatation in children remains controversial,(13) with sparse published information on outcomes for syndromic presentations.(19, 20)

The aims of our study were 1) to describe the clinical findings, therapeutic interventions and long-term outcome, including nutritional status of children with achalasia, 2) and contrast the outcome of initial treatment with myotomy as against botulinum toxin. 3) We also sought to determine if an association with triple A syndrome influenced diagnosis or outcome.

METHODS

Patients treated for achalasia at The Royal Children's Hospital Melbourne from 1982 to 2013 were identified from hospital information systems. The diagnosis was confirmed in the presence of typical findings on barium swallow and oesophageal manometry, and in the absence of any other cause established by upper gastrointestinal endoscopy.

Details of primary and secondary therapeutic interventions were recorded. These included oesophageal myotomy, pneumatic dilatation , endoscopic intra-sphincteric injection of Clostridium botulinum toxin type A (Botox, Allergan Australia Pty Ltd, Gordon, NSW, Australia),(14, 16) and the use of calcium channel blockers.

Failure to respond to treatment or recurrence of symptoms was defined as symptoms occurring on a daily basis, consistent with achalasia and interfering with global quality of life. Subsequent interventions were documented as were the outcomes and complications.

Long term outcome was determined by questionnaires which were mailed to last known addresses.

Analysis

Normally distributed data are presented as mean ± standard deviation, or as median and interquartile range (IQR) if skewed. Analyses were performed using GraphPadPrism 5 (GraphPad Software Inc. La Jolla, CA, USA) using tests for normally distributed or non-parametric data as appropriate.

Ethical considerations

The Royal Children's Hospital Human Research Ethics Committee approved project HREC33226. Informed consent was obtained from all patients completing the questionnaire.

RESULTS

Demographics

Forty-two children (21 male) were identified with achalasia during the study period. The median age at diagnosis was 10.8 years (IQR 7.8, 13.1), duration of symptoms prior to diagnosis 233 days (IQR 146, 617) and follow up 1593 days (IQR 391, 3143).

Six patients were diagnosed between 1982-1993, 15 from 1994-2003 and 21 from 2004-2013.

Associated syndromes/disorders

Nine of 42 (21%) had an associated syndrome or chromosomal abnormality (triple A syndrome n=6, trisomy 21 n=2). Another infant had a complex chromosomal abnormality (deletion of 8p23.3p23.1, duplication of 12p13.33p13.31).

Presenting symptoms and diagnostic investigations (Table 1)

The main symptoms were: regurgitation of poorly digested food, dysphagia, weight loss and vomiting.

All had undergone upper gastrointestinal barium contrast studies and gastroscopy with biopsies. Thirty-eight underwent manometry with two too young to tolerate the procedure, and in two patients the result was unavailable.

Management:

Primary surgical treatment - outcome (Figure 1)

Seventeen of the 42 patients underwent a myotomy as first-line treatment. Persistent or recurrent symptoms in 11 (65 %) required further interventions after a median 1993 days (IQR 223, 2196). Of these 11, 5 received botulinum toxin after the initial failed myotomy, and 5 had a pneumatic dilatation. Two of the 5 who received botulinum toxin as a secondary treatment had a sustained response, whereas 4 of the 5 who received a pneumatic dilatation as a secondary treatment had a sustained response (p=0.52). Five of the 11 children (41 %) ultimately underwent a second myotomy.

Primary non-surgical treatment - outcome (Figure 2)

Twenty-four patients had non-surgical primary treatment (botulinum toxin [n=20], pneumatic dilatation [n=3] or a calcium channel blocker (nifedipine) [n=1]). One patient did not receive any treatment.

Further injections of botulinum toxin were provided if symptoms recurred. The median total number of additional botulinum toxin injections per patient was 2.0 (IQR 1.8, 6.5) and maximum 15. No complications were recorded in the patient records for the 112 botulinum toxin injections. At the time of this report, 3 of these 20 patients had transitioned to adult care without receiving alternative therapies after 11, 10 and 5 years of botulinum toxin treatments. Of the 17 other patients, all ultimately underwent a Heller's myotomy as a

subsequent procedure, which had to be repeated in five patients. The median interval before receiving an alternative intervention was 434 days (IQR 69, 1367).

Of the 17 patients who underwent a myotomy after botulinum toxin, 3 had a major complication in the immediate post-operative phase. Two had gastric perforations and one child developed a pneumomediastinum.

Myotomy and Botulinum toxin as primary procedures – outcome (Figures 3, 4)

Seventeen of 20 (85%) of patients who had botulinum toxin injections as their first treatment subsequently received an alternate form of therapy. This occurred after a median 434 days. By comparison, where a myotomy was provided as the first treatment, 11 of 17 (65%) received further therapy after a median 1993 days (fig 4). Neither the proportion who failed to achieve a sustained response, nor the interval before a secondary treatment was administered, was significantly different between the two groups (p=0.46, p=0.22 respectively).

Overall, 35 patients underwent a myotomy either as a primary or subsequent procedure. In 27/41 patients, a myotomy was the final intervention provided, but 10 patients required 2 myotomies.

The likelihood of proceeding to a second myotomy was not influenced by the primary treatment. Of those patients who had an initial myotomy, 5/17 required a repeat myotomy.

Of those who had botulinum toxin initially but then proceeded to a myotomy, 5/15 required a repeat myotomy.

Eight surgeons operated on the patients over 30 years, with one performing 21 of the 40 procedures. Comparison of the outcomes of this surgeon with those of the other 7 with regard to need for repeat myotomy, showed no statistically significant differences (31 % vs 26 %, p=0.84).

Number of interventions and subsequent duration of response

Excluding repeated injections of botulinum toxin, 84 interventions were performed on 41 patients. Myotomy was the preferred "second-line" therapy (n=16), with botulinum toxin being used in 8 patients, and pneumatic dilatation in 6. When a third type of intervention was administered, myotomy was preferred (n=7), with 3 receiving pneumatic dilatation.

Two patients underwent a fundoplication for reflux as part of a myotomy as a second or third intervention.

Nutritional status

The mean weight-for-age Z-score (WAZ) at presentation was -1.05 ± 1.53. This had improved significantly after all treatment interventions had been completed (WAZ -0.74 ± 1.49; p<0.005).

The type of initial intervention, myotomy or botulinum toxin, did not impact on the ultimate likelihood or extent of a statistically significant WAZ gain.

Triple A syndrome

Patients with triple A syndrome (n=6) developed their first symptoms significantly earlier than those who did not have either a syndrome or recognised chromosomal abnormality (n=33; 5.2 ± 3.7 yr vs 9.7 ± 3.8 yr; $p<0.05$). These symptoms were present for longer before the diagnosis was achieved (549 ± 510 days vs 328 ± 340 days; $p<0.01$). There was no significant difference between the two groups in types of presenting symptom. However, those with triple A syndrome were significantly more underweight at diagnosis (WAZ -2.9 ± 1.6 vs WAZ -0.6 ± 1.2; $p<0.001$).

The choice of initial therapy was similar for the two groups, whether Heller procedure (1/6 vs 15/33) or botulinum toxin (3/6 vs 16/33). Where botulinum toxin was used, both had a similar number of treatments (4.7 ± 3.6 vs 3.9 ± 4.1; $p=0.42$). However, there was a suggestion that those with triple A syndrome waited a longer time before receiving a second therapy (triple A 1670 ± 1639 days vs 732 ± 1071 days; $p=0.068$).

Patients with triple A syndrome achieved significant weight gain between diagnosis and at last follow up (mean improvement in triple A WAZ 1.25 ± 1.11; $p<0.05$). However, their mean weight remained significantly less than the general population after a mean follow up period of 4363 ± 3100 days (WAZ -1.67 ± 1.77; $p<0.05$). In those without a syndromic or

chromosomal association the mean change in WAZ after treatment was 0.40 ± 1.03 (p=0.07). Their WAZ at last recorded follow up (after a mean 1800 ± 1640 days) was -0.46± 1.39.

Questionnaire

Questionnaires were sent to 42 patients or families, but 30 did not respond, 3 refused to participate, one patient had died of unrelated causes and only 8 were completed and returned. The mean age at completion of the questionnaire was 18.6 ± 3.7 yr (5M:3F).

Apart from one patient, who was still receiving regular botulinum toxin injections, all had either initially or ultimately undergone a Heller's myotomy. The median interval since the myotomy (or repeat procedure if necessary), was 43 mo (IQR 7.5, 94.4).

All but one of the 8 patients was still seeing a medical practitioner regularly, either monthly (n=1), 6 monthly (n=3), or annually (n=3). Episodes of "food-sticking in the throat" occurred daily in 6 out of the 8 or at least weekly in the other two. Five of the eight patients who completed the questionnaire reported difficulty in eating in public or with their peers. Chest pain was experienced daily by 3, at least weekly by 2 and at least monthly by 3 of the 8. Regurgitation was present on a daily basis for 2 patients, weekly for 1, 2 monthly for 2 but hardly ever in 3 of the 8. Their mean BMI was 19.5 ± 2.6, but two of the patients aged over 18 were underweight with a BMI less than 18.5 (15.4, 17.8).

Five of the eight reported that achalasia had a significant impact on their quality of life. Complete avoidance of social gatherings was reported by four of the five patients. Three of the five patients had been diagnosed with an anxiety disorder. One patient reported that his significant weight loss was traumatic for his parents, because of accusations by the community and health care workers that they had been underfeeding him.

DISCUSSION

Forty-two patients with achalasia were identified, corresponding to an identification rate of approximately 0.13 per 100,000 children aged less than 16 years. This is similar to the incidence rate identified in the UK (0.18 per 100,000 people aged less than 16yr)(1) and suggests a high rate of recruitment.

Our study has confirmed that no one therapeutic approach was universally successful and that the outcome is generally disappointing no matter what the primary intervention Historically, while myotomy has been the usual approach, two-thirds of patients who underwent a primary myotomy subsequently had a further procedure. A limitation of the retrospective nature of this study is that failure of the initial procedure was judged by the provision of a secondary procedure. There may have been more patients with recurrent symptoms who did not undergo further procedures. The median interval before a secondary treatment was carried out – nearly 6 years – suggested protracted symptoms, or perhaps progressive disease. Alternative therapies such as botulinum toxin were not available for the earlier patients in this cohort. Relatively small numbers of patients in each

decade group precluded a detailed statistical analysis for type of intervention by era of surgery.

Botulinum toxin, used as a primary therapy in half of the patients, had a temporary impact with most patients ultimately proceeding to a myotomy. About one third of this group then required still further surgery after the first myotomy. There were no significant complications associated with the botulinum toxin treatments themselves.

Gastric perforation or pneumomediastinum occurred after myotomy in 18% of those initially treated with botulinum toxin. An increased risk of complications after prior endoscopic therapy with either botulinum toxin or pneumatic dilatation has previously been suggested,(4, 21) but both intraoperative oesophageal and gastric perforations are well recognised even during primary myotomy uncomplicated by prior interventions, occurring in about 6% of procedures.(4) These are usually repaired intraoperatively without clinical consequence.

Most children were significantly underweight by the time they had surgery, but this improved significantly after both myotomy and botulinum toxin injection.

Pneumatic dilatation was also provided in this group of patients, but too few to enable statistical inference. Recent trials of pneumatic dilatation against myotomy have suggested the two are broadly comparable.(22)

Some authors suggest that up to 90% of patients treated for achalasia can achieve near normal swallowing and quality of life after a combination of current treatments.(23) The difficulty is that even in those centres reporting large cohorts, most patients need multiple further treatments.(4) The disease is also progressive. Evidence suggests that manometric subtyping can help predict likelihood of response to surgery.(24) Patients with type III disease appear to respond better to Heller myotomy than pneumatic dilatation, whereas there is little difference between the two for type I and II disease.

Our attempt to evaluate long term outcome for quality of life was hampered by poor recruitment. This might have been improved by a second mailout or direct telephone contact, but of those who did respond most were not doing well, with persistent symptoms, a poor quality of life and significant underweight. It may be dangerous to extrapolate from this small group, but it would be safe to say that significant symptoms do appear to persist in at least a small proportion, with long term impact on the family and patient. Other studies have also found a substantial impact of achalasia on quality of life in children.(25) It would be helpful to assess this in more detail with fully validated measures. The reason for the poor response rate was unclear.

About 15% of our patients also had triple A syndrome. This has been associated with mutations in the AAAS gene on 12q13 which codes for a protein called ALADIN (alacrima-achalasia-adrenal insufficiency neurologic disorder)(3) which is important in structural scaffolding of the nuclear pore complex. We and others found evidence of delayed

diagnosis of achalasia in patients with triple A syndrome.(19) They were significantly underweight at diagnosis and at last follow up. Whether this was related to the syndrome itself or was a legacy of the prolonged malnutrition prior to diagnosis and treatment is not clear. Ttheir response to treatment appeared no different to other children. This may well represent a high risk group who merit close postoperative follow up with nutritional rehabilitation. Reasons for the delayed diagnosis are unclear. Typically, the "classic presentation" is of an infant who is first noted to not make tears on crying , develops ACTH-resistant adrenal insufficiency in the first decade of life and goes on to be diagnosed with achalasia in the first or second decade.(19) Gastro-oesophageal reflux may be inappropriately diagnosed. Clearly, the identification of alacrima and adrenal insufficiency should lead to early manometric evaluation for oesophageal dysfunction. There is no evidence in the literature(3, 5, 19) or from our studies that the subsequent management of achalasia associated with triple A syndrome should be any different from standard approaches.

There are no clear paediatric-specific recommendations for treatment of children with achalasia, but there is increasing agreement in adult practice for treatment pathways which do inform therapeutic decisions in children.(26) Healthy patients with achalasia should receive either graded pneumatic dilatation or myotomy. Myotomy is likely to be more effective treatment in adolescents and younger adults, especially men and possibly patients with type III achalasia. Women and older adults do well with either myotomy or pneumatic dilatation. It is not clear if these same gender implications exist in children. Botulinum toxin

should be the first line treatment in frail patients because it is safe and likely only to be needed to be repeated every 9-12 months. Pneumatic dilatation has also been suggested as a safe alternative for frail patients but with the caveat it be used in high volume centres, which excludes most paediatric units. Although there is experience of using the promising(27) and more recently introduced per oral endoscopic myotomy (POEM) in children,(8) its role has yet to be more closely defined.

It has been argued that routine post-operative manometric evaluation should be used to help predict outcome and better define those patients who are likely to need further intervention.(4) The following functional parameters have been associated with poor outcome after treatment in adults: 1) failure to empty the oesophagus of barium after 5 minutes upright, 2) failure to completely relieve symptoms after the primary intervention, 3) post-procedure lower oesophageal sphincter pressures greater than 10-15mmHg, and 4) limited distensibility of the esophago-gastric junction.(4)

We have confirmed that the long term functional outcome after current treatments for achalasia is less than optimal. Some patients undergo long periods of persistent or recurrent symptoms which might benefit from earlier targeted interventions. There is a strong case to be made for the routine evaluation of physiological function after treatment of achalasia in children to help inform and guide subsequent interventions, particularly in high risk clinical subtypes.

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Table 1: Presenting Features

Symptom or clinical feature	**n=42 (%)**
Regurgitation of poorly digested food	34 (83%)
Dysphagia	31 (76%)
Weight loss	31 (76%)
Vomiting	27 (66%)
Nocturnal cough	23 (56%)
Recurrent respiratory infections	16 (39%)
Chest pain	14 (34%)
Choking	13 (32%)
Alacrima	7 (17%)
Addison's disease	5 (12%)
Nausea	2 (5%)

Figure Legends

Figure 1.

Outcome after myotomy as a primary procedure.

Figure 2.

Outcome after a non-surgical primary approach.

Figures 3 and 4.

Proportion of patients proceeding to further treatment because of failure of the initial therapy with either myotomy or Botulinum toxin by 1 year (figure 3) and 10 years (figure 4). There was no significant difference in the median interval before subsequent treatment (log-rank test; p=0.15).