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Childhood achalasia: A comprehensive review of disease, diagnosis and therapeutic management

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MINIREVIEWS

Childhood achalasia: A comprehensive review of disease, diagnosis and therapeutic management

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Abstract

Achalasia is an esophageal motility disorder characterized by failure of lower esophageal sphincter (LES) relaxation and is rare in children. The most common symptoms are vomiting, dysphagia, regurgitation, and weight loss. Definitive diagnosis is made with barium swallow study and esophageal manometry. In adults, endoscopic biopsy is recommended to exclude malignancy however; it is not as often indicated in children. Medical management often fails resulting in recurrent symptoms and the ultimate definitive treatment is surgical. Laparoscopic Heller myotomy with or without an anti-reflux procedure is the treatment of choice and has become standard of care for children with achalasia. Peroral endoscopic myotomy is a novel therapy utilized with increasing frequency for achalasia treatment in adults. More experience is needed to determine the safety, efficacy, and feasibility of peroral endoscopic myotomy in children.

Key words: Achalasia; Pediatrics; Surgical Heller myotomy; Balloon dilatation; Lower esophageal sphincter

Core tip: Achalasia is a neurodegenerative disorder of the lower esophageal sphincter which occurs less commonly in children compared to adults and patients present with progressive dysphagia, vomiting, and weight loss. Medical therapy including botulinum toxin injection and endoscopic dilatation have been associated with only transient relief of dysphagia symptoms as is also seen in adults. While current evidence also suggests that the surgical approach of laparoscopic Heller myotomy provides lasting benefits for children with achalasia, future prospective evaluation will need to be conducted to ascertain whether peroral endoscopic myotomy is safe and equally effective in children.

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INTRODUCTION

Achalasia is a rare esophageal neurodegenerative disorder in the pediatric population. The disease is even more infrequent in children less than 5 years of age. The incidence of achalasia in childhood is 0.11/100000 children annually[1,2]. Overall, less than 5% of patients with symptoms present under the age of 15[3]. The disease is more prevalent in males and is most commonly idiopathic. Achalasia has been associated with Trisomy 21, congenital hypoventilation syndrome, glucocorticoid insufficiency, eosinophilic esophagitis, familial dysautonomia, Chagas' disease, and achalasia, alacrima, and ACTH insensitivity (AAA) syndrome[3].

Failure of the lower esophageal sphincter to relax

leads to the sequelae of achalasia. The pathophysiologic basis of achalasia is characterized by the degeneration of the inhibitory myenteric plexus that innervates the lower esophageal sphincter (LES) and esophageal body[4]. This leads to an imbalance in the inhibitory and excitatory neurons resulting in the failure of the LES to relax with swallowing, absence of peristalsis of the esophageal body, and increased LES resting pressures[5]. Goldblum *et al*[6] found a depletion or absence of myenteric ganglion cells, destruction of myenteric nerves, and chronic myenteric inflammation in 42 esophageal specimens. It is supposed that abnormalities in the parasympathetic innervation of the esophagus result in the esophageal dysmotility seen in achalasia; however the precise etiology of this abnormality is unclear[7].

Children usually present with progressive dysphagia, vomiting, and weight loss. Younger children and infants may also present atypically with recurrent pneumonia, nocturnal cough, aspiration, hoarseness, and feeding difficulties[3,8]. Achalasia in children is often misdiagnosed as gastroesophageal reflux disease (GERD). Children frequently present with failure to thrive, eating disorders, eosinophilic esophagitis, or asthma, which then leads to a delay in diagnosis for as long as 6-10 years[3]. Up to 50% of children are treated with antacids or prokinetics before the diagnosis of achalasia is identified[2].

DIAGNOSIS

Achalasia is diagnosed with a barium swallow study and may be confirmed with esophageal manometry. Barium swallow studies classically demonstrate a dilated esophagus with "bird's-beak" like tapering of the distal esophagus. Often, since there is a significant delay in diagnosis of achalasia in children, the esophagram study alone is diagnostic. Elevated resting LES pressure, absent or low-amplitude peristalsis, or non-relaxing LES upon swallowing are diagnostic findings on esophageal manometry in children with achalasia[1,2]. However, absence of these findings does not rule out the diagnosis of achalasia since LES function in children is heterogeneous. Partial relaxations are common and normal relaxations may also be present on manometry according to Morea *et al*[8]. Upper endoscopy and biopsy is reasonable to rule out esophagitis, Trypanosoma cruzi, malignancy, and other secondary causes of achalasia[1,4,5]. Our institutional protocol for work up consists of a barium swallow study, upper endoscopy, and endoscopic biopsy.

The various methods of treatment of achalasia involve reduction of LES pressure in order to facilitate esophageal emptying by: injection of botulinum toxin, oral administration of calcium channel blockers (Nifedipine), pneumatic dilatation, or esophageal myotomy (Heller) with or without an anti-reflux procedure.

MEDICAL THERAPY

Nifedipine, a calcium channel blocker, inhibits the trans membrane calcium influx in cardiac and smooth muscle and has been primarily used to treat achalasia in adults[5]. In children, the use of nifedipine has not been well studied. Maksimak *et al*[9] reported 4 children treated with nifedipine before meals who reported relief of symptoms likely related to a decrease in resting LES pressure. In either children or adults, nifedipine is not a definitive therapy and should only rarely be used as a bridge to relieve symptoms until pneumatic dilatation, Botox injection or myotomy can be performed[5,10].

ENDOSCOPIC THERAPY

Botulinum toxin injected into the LES acts on the excitatory terminal nerve endings of the myoneural junctions preventing acetylcholine release. Acetylcholine releasing neurons function in influencing the basal muscle tone[1]. Injection of botulinum toxin into the LES can be both diagnostic and therapeutic. Optimal dosing and injection frequency of botulinum toxin to relieve achalasia symptoms in children has not been well defined. After botulinum injection, the mean duration of symptom relief is 4 months, often requiring multiple treatments within a year[11]. In addition, botulinum toxin injection only provides permanent relief in 10%-40% of cases in adult patients[12] thus, will often require definitive surgical management.

PNEUMATIC DILATATION

Pneumatic dilatation or dilation of the functionally obstructed esophagus has been used in children. Recommended balloon sizes in children > 8 years is 35 mm[13,14]. Multiple dilatations are often required to achieve successful relief of symptoms although initial response predicts the success or failure of subsequent dilatations[15]. Hamza *et al*[14] reported a 90% success rate in children treated with multiple pneumatic dilations. The advantages of balloon dilatation include shorter length of stay, quicker recovery time, and decreased cost[13]. Pneumatic dilatation can be complicated by substernal pain, prolonged epigastric pain, esophageal perforation, aspiration pneumonia, and GERD[13,16-19]. Multiple studies suggest that in older children, pneumatic dilation is effective and safe initial treatment for achalasia and may spare children with achalasia an operation[13,14,20]. There are no long-term follow up studies in children to document success rates of pneumatic dilatation for achalasia. For adult patients, Eckardt *et al*[21] reported recurrence rates in as high as 60% in patients who underwent a single pneumatic dilation. Recurrent symptoms in children following multiple dilatations may require surgical myotomy[17,18,22].

SURGICAL

Despite multiple treatments for achalasia, surgery is the most definitive and successful treatment of choice. Laparoscopic Heller myotomy (LHM) involves making

Table 1 Patient demographics

	Mean	
Gender		
Female	13	54%
Male	11	46%
Age of diagnosis	11	5-18
Duration of symptoms	2.8 years	1-11 years
Presenting symptoms	*n*	Percentage
Dysphagia	20	83%
Emesis	14	58%
Weight loss	11	46%
Chest pain	10	42%
Regurgitation	4	17%
Odynophagia	2	8%

Table 2 Surgical approach

	Mean	
Age at surgery	12.9	5-8
OR time	124 min	45-213 min
LOS	2.7 d	1-6 d
Follow up	3.5 mo	1-12 mo
	n	Percentage
LHM	3	12.50%
LHM + TF	2	8.30%
LHM + DF	19	79.20%

LOS: Length of stay; LHM: Laparoscopic Heller myotomy; TF: Thal fundoplication; DF: Dor fundoplication.

a longitudinal incision in the muscle of the esophagus approximately 5 cm above the esophagogastric junction and extending 2-3 cm onto the cardia of the stomach. Laparoscopic Heller myotomy in children as in adults is the surgical treatment of choice[20,23-26].

Over the last 8 years at our institution, 24 patients were diagnosed with achalasia that subsequently underwent surgical treatment. Forty-six percent of the patients were male with a mean age of 11 (5-18 years). (Table 1) In this patient population, associated comorbidities included: mixed connective tissue disease scleroderma (1); Down's syndrome (1); inflammatory bowel disease (1); Sjogren's syndrome; and Pott's disease (1). The most common presenting symptoms were dysphagia (83%), emesis (58%), weight loss (46%), and chest pain (42%). Average weight loss was 9.9 kg requiring supplemental nutrition. Mean duration of symptoms prior to surgical treatment was 2.8 years, which was consistent with multiple studies[16,26-31]. Upper endoscopy in our patients commonly showed a dilated esophagus with retained food products. Approximately one-third of our patients had an abnormal biopsy. Four patients had acute esophagitis one of which was treated for Candida. Esophageal manometry was done in only 38% of our patients secondary to inability to tolerate the procedure. Only 2 patients (8%) who underwent myotomy were treated with nifedipine with only temporary relief of symptoms. Four underwent pneumatic dilatation (17%). In 1 patient, pneumatic dilatation was complicated by esophageal perforation requiring video-assisted thoracoscopic surgery (VATS) drainage and prolonged hospital stay. This patient subsequently underwent a laparoscopic Heller myotomy (LHM) and Dor fundoplication with resolution of symptoms of achalasia at 3 month follow up. Most of our patients (88%) underwent laparoscopic Heller myotomy with a Dor or Thal fundoplication. Average age at the time of surgical treatment was 12.9 years of age (5-18) (Table 2). Average operating time was 124 min.

In our series, we had only 2 intraoperative mucosal perforations, which were repaired primarily laparoscopically in children that had had LHM without fundoplication. Two children who had LHM with Thal fundoplication developed recurrent dysphagia requiring pneumatic dilations several months later. One patient who underwent a LHM and Dor fundoplication required a laparoscopic redo LHM and Dor for recurrent dysphagia. All of our patients receive a barium swallow study and a clear liquid diet on the first postoperative day. We have had no incidence of leak on the esophagram in our patients postoperatively or delayed perforations. We routinely discharge our patients on postoperative day 2 and our average length of stay is 2.6 d. Eight percent of our patients had recurrent symptoms of dysphagia postoperatively. One patient required revision of the initial operation 10 mo after the first operation (Table 3). There was a significant improvement in symptoms after the second procedure. As seen in other centers, most patients with recurrent dysphagia after surgical treatment for achalasia undergo balloon dilatation with improvement in their symptoms (Table 3).

The laparoscopic approach is superior to the open approach secondary to the well-recognized benefits including minimal pain, better cosmesis, shorter hospital stay, and faster return to normal activity for the child and parent/guardian[26]. Common causes of surgical failure are GERD and recurrent dysphagia. A partial fundoplication is commonly used to prevent GERD in patients following Heller myotomy. In a randomized controlled trial, Rebecchi *et al*[32] determined that laparoscopic Dor fundoplication after a LHM was superior to Nissen fundoplication because the recurrence rate of dysphagia was significantly higher in patients who received a Nissen fundoplication in their adult patients. There is some controversy as to whether an anti-reflux procedure should be performed in children at the time of LHM. Corda *et al*[24] concluded that an anti-reflux procedure is not required with a LHM for the prevention of GERD. Other studies have shown benefits and it is our practice to perform LHM and partial fundoplication[27,28,31,33].

The two primary complications of surgical management of achalasia are esophageal perforation and recurrent dysphagia. In our experience and review of

Table 3 Surgical management of pediatric achalasia

Ref.	*n*	Age (yr)	Symptom duration (mo)	Procedure	OR time (min)	Complications	Treatment	Length of stay (d)	Follow up (mo)
Pastor *et al*[16]	40	12.4	10.7	6 OHM 3 LHM 11 LHM + Nissen 21 dilation	186 156	1 perforation 2 perforations	Sutured Sutured	- -	75
Corda *et al*[24]	20	12 (5-15)	24	20 LHM	96 (60-160)	4 conversions OHM 5 dysphagia	 1 lap LOA 1 redo LHM 1 redo OHM	3 (1-5)	60
Esposito *et al*[26]	31	8.4 (5-15)	>12	31 LHM/Dor	120	3 perforations 5 dysphagia	2 sutured 1 redo HM 2 dilated 1 redo OHM	4 (3-8)	9-156
Tannuri *et al*[27]	15	12 (9-17)	30	15 LHM/Dor	90 (150-260)	2 dysphagia	1 botox injection	2.5 (1-4)	32.5 (2-96)
Patti *et al*[28]	13	15 (6-17)	24	13 LHM/Dor	144 ± 35	-	-	2	19
Lelli *et al*[29]	19	10 (1-17)	-	14 OHM 5 OHM + Belsey	-	2 dysphagia	2 dilation	8	108 (6-252)
Rothenberg *et al*[30]	9	12 (5-17)	6-24	4 THM 5 LHM/Dor	95 62	1 perforation 1 dysphagia 2 GERD 1 delayed perforation	Sutured Redo LHM Medical Rx Lap repair	2 1	-
Askegard-Giesmann *et al*[31]	26	15 (4-18)	-	1 LHM 2 LHM/Dor 23 LHM + Toupet	- 	1 perforation 1 perforation/aspiration 7 dysphagia 1 GERD	Sutured Sutured 3 redo LHM 3 dilation 1 botox Medical Rx	2.7 (1-4)	0-75 -20
Esposito *et al*[32]	8	6.3 (2-13)	> 121 LHM	6 LHM/Dor 2 LHM/Thal	120 (90-150)	3 perforations	3 sutured	4 (3-31)	6-60
Current Study	24	12.9 (5-18)	> 24	3 LHM 2 LHM/Thal 19 LHM/Dor	124 (45-213)	2 perforations 2 dysphagia	2 sutured 2 dilations 1 redo LHM	2.7 (1-6)	4 (4-24)

OHM: Open Heller myotomy; LHM: Laparoscopic Heller myotomy; THM: Thoracosopic Heller myotomy; Rx: Therapy.

the literature, there was 0%-26% recurrence rate of dysphagia after LHM with or without an anti-reflux procedure (Table 3)[16,24,26-30,33]. It is unclear if recurrent dysphagia is secondary to the nature of disease or failure of surgical treatment. Surgeon experience may contribute to decreasing rates of complications as suggested by Esposito *et al*[26] since their incidence of post-operative dysphagia dropped from 50%[33] to 16% with further experience. Our incidence of recurrent dysphagia is 8% compared to 11%, 16%, 25%, and 26%[29,25,26,31] in comparable sized series (19-31 patients). Perforation rates occur from 0%-15% (8% in ours) in larger series[16,24,29,31] but rarely require re-operation (Table 3). Accordingly, in smaller series and those from longer time periods in the past, perforation rates were higher (22%-50%) probably related to the establishment of a learning curve for the operation[30,33].

PER ORAL ENDOSCOPIC MYOTOMY

Peroral endoscopic myotomy (POEM) is a novel technique in the treatment of achalasia. POEM is one of few procedures utilizing natural orifice transluminal endoscopic surgery (NOTES) routinely in adults. POEM is an endoscopic procedure that directly treats the diseased tissue[23]. Pasricha *et al*[34] first described a submucosal endoscopic esophageal myotomy in animal studies for the treatment of achalasia. Inoue *et al*[35] coined the term peroral endoscopic myotomy and was the first to perform the procedure in 17 adult patients. Multiple studies have concluded that short-term outcomes of this procedure were safe[35-38].

Not all patients are suitable candidates for POEM. Contraindications include severe pulmonary disease, coagulation disorders, prior esophageal mucosal resection, or any prior therapy that has compromised the integrity of the esophageal mucosa[37]. POEM is performed utilizing flexible endoscopy, mucosal incision and dissection of a submucosal tunnel distally in the esophageal wall to approach the esophagogastric junction. A 2-3 cm longitudinal incision in the inner circular muscle approximately 4 cm from the LES, will produce similar results to

Heller myotomy[36,38]. A contrast esophagram is routinely obtained on the first postoperative day and the patient is started on a pureed diet if esophagram is normal[36-39].

Ren *et al*[40] reported 119 cases of achalasia treated with POEM, the most common postoperative complications included subcutaneous emphysema (55.5%), pneumothorax (25.2%), pneumomediastinum (29.4%), pleural effusion (48.7%), segmental atelectasis (49.6%), pleural effusion (48.7%), and pneumoperitoneum (39.5%). In this study, 13 patients with pneumothorax were treated with thoracic drainage and 2 patients with pleural effusion were treated with thoracentesis. The high incidence of pneumothorax, pneumomediastinum, subcutaneous emphysema, and pneumoperitoneum was attributed to the use of air insufflation during the procedure and subsequently this group now utilizes CO_2 insufflation[23]. Swanström *et al*[36] reported pneumoperitoneum in 3 out of 5 patients that were treated with Veress needle. Inoue and associates reported pneumomediastinum in multiple patients, however these patients did not require treatment although another patient in that series underwent thoracostomy drainage tube placement[39]. Feasibility of POEM is highly dependent on surgeon' s experience, duration of symptoms, prior pneumatic dilatations, and endoscopic therapies[41]. Nonetheless, multiple studies have reported POEM provides favorable outcomes and is relatively safe for the treatment of achalasia in adults[35-37,39-43]. Long-term outcomes (> 6 mo) for POEM in adult patients have been reported by Swanström *et al*[44] as significant in relieving dysphagia in 83%. Maselli *et al*[45] reported the first case of POEM performed in a 3-year-old with achalasia complicated by failure to thrive. At 1-year follow up, the patient was asymptomatic and had an appropriate weight for her age[45]. Familiari *et al*[46] reported 3 children treated with POEM for achalasia. There were no postoperative complications. In this study, 2 out of 3 patients had complete resolution of symptoms and the third patient had improvement in symptoms after 1-year follow up[46]. Although POEM is effective, minimally invasive, and safe in adults, there is also more recent evidence to suggest that the surgical approach (laparoscopic Heller myotomy) is more definitive and long lasting in relieving symptoms in these patients compared to endoscopic dilatation or botulinum toxin injection techniques[47]. It is apparent that effective therapy for children with achalasia is needed. Marlais *et al*[48] reported that children with achalasia have a significantly lower quality of life (QOL) compared to both children with inflammatory bowel disease and healthy children. While current evidence also suggests that the surgical approach provides lasting benefits for children with achalasia, future prospective evaluation will need to be conducted to ascertain whether POEM is safe and equally effective in children. For now, it is unclear; however pediatric surgeons are interested in learning this novel technique and employing its use in the management of pediatric achalasia.

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