Pediatric Achalasia

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Introduction

Achalasia is a rare entity in the pediatric population. It is estimated to affect between 0.11 and 0.18/100,000 children annually [1, 2]. It can occur as young as 7 weeks of age, but children under 15 years of age account for less than 5 % of all achalasia cases [3-6]. As in adults, pediatric achalasia is most commonly idiopathic and isolated; however, it occurs infrequently in the setting of genetic and familial conditions. Symptoms of vomiting, progressive dysphagia, and weight loss are a result of failure of relaxation of the lower esophageal sphincter (LES), impaired peristalsis, and increased LES resting pressures [7, 8]. Diagnosis and treatment are similar to adults, with no curative treatment available, but a number of different options for symptom palliation.

For the majority of children with achalasia the pathophysiology is the same as adults, with some histologic studies suggesting an autoimmune component [9], but children may also develop

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this in the setting of genetic conditions. Familial achalasia is extremely rare, with case reports of parent and child with achalasia and multiple siblings from consanguineous relationships affected suggesting an autosomal recessive inheritance [10–13]. Genetic analysis of one set of siblings demonstrated a mutation in nitric oxide synthase, requiring sildenafil treatment after failure to improve with cardiomyotomy [11]. Achalasia may also occur in the setting of multiple syndromes including Allgrove's syndrome, Sjogren's syndrome, Rozychi's syndrome, and Down's syndrome [14–16]. Since Allgrove's first description of patients with achalasia, alacrima, and adrenal insufficiency in 1978, there have been multiple reports of patients with Triple A syndrome [16]. Also known as Allgrove syndrome or 4A syndrome (including autonomic disturbance), children may present first with achalasia, necessitating careful clinical evaluation for signs of hyperpigmentation and abnormal lacrimation that may allow treatment before life-threatening complications of adrenal insufficiency develop [10, 17, 18]. There is no consensus as to the optimal therapy for patients with Triple A syndrome, but multiple reports show improvement with esophageal cardiomyotomy with or without partial fundoplication [10, 19]. Heller's myotomy has also been successful for the rare children who develop achalasia in the setting of Down's syndrome [3, 14]. One recent series of three pediatric achalasia patients suggests a possible association

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with autism, highlighting the need for evaluation of autistic children suffering from eating disorders or esophageal symptoms with barium swallow and manometry [20].

The rarity of achalasia and presence of symptoms that mimic common pediatric diagnoses may lead to misdiagnosis in children with this disease. Achalasia symptoms often mimic those of gastroesophageal reflux disease (GERD) in younger children who present with failure to thrive, feeding difficulties, and recurrent pneumonia [5, 21]. This atypical presentation can lead to a delay in diagnosis anywhere from a few months to more than 5 years [5]. Confounding the picture, GERD has also been reported in some series to accompany or precede achalasia, leading to recommendations to consider high-resolution manometry (HRM) in those children who do not respond to initial reflux treatment [22]. Given the relative frequency of GERD compared to achalasia, up to 50 % of children are treated with prokinetic or antacid medications prior to receiving a definitive diagnosis of this condition [5, 7]. A study of Brazilian children revealed that many patients are misdiagnosed with asthma, with 46 % of those eventually diagnosed with achalasia receiving ineffective asthma therapy for chronic cough that resolved with esophageal myotomy or pneumatic dilation [5]. In three children thought to have refractory asthma, the diagnosis was only suspected once tracheal obstruction was identified on pulmonary function testing, leading to further work-up with diagnosis and successful treatment of their achalasia [23-25]. Achalasia can also be confused with eosinophilic esophagitis, with one study reporting elevated intraepithelial eosinophils in 34 % of patients, and 8 % meeting criteria for eosinophilic esophagitis [26]. Common symptoms have also contributed to multiple reports of adolescents and children diagnosed and treated for eating disorders, (both anorexia nervosa and bulimia) who were eventually diagnosed and successfully treated for esophageal achalasia [5, 27, 28]. These highlight the need to fully evaluate children with dysphagia, even if symptoms suggest a psychiatric etiology.

Importantly, esophageal dysmotility and distension have been misdiagnosed as achalasia in multiple adolescents who were eventually diagnosed with an H-type trachea-esophageal fistula [29–31]. H-type fistulas can cause chronic overdistension of the esophagus and affect peristalsis, leading to the diagnosis of achalasia, but not necessarily requiring any other treatment once the fistula is closed [31].

Diagnostic Workup

Diagnosis of achalasia in children is made by a combination of careful history and symptom review, barium swallow study and if necessary, esophageal manometric studies. Upper endoscopy should also be considered to exclude other potential causes of dysphagia.

Barium Swallow Study

Barium studies typically demonstrate proximal esophageal dilatation, with a "bird's beak" narrowing distally at the level of the contracted lower esophageal sphincter [5]. This can be especially apparent in type 1 achalasia cases or where there has been a significant delay in diagnosis, and is diagnostic in approximately 2/3 of pediatric cases [32]. Barium swallow may not be diagnostic in types 2 and 3 achalasia (using the Chicago Classification); therefore further testing with high resolution manometry may be needed to make the diagnosis [33].

Esophageal Manometry

Esophageal manometry, the gold standard for diagnosis, classically demonstrates increased LES resting pressures, impaired esophageal peristalsis, and abnormal relaxation of the LES with swallowing [5, 34, 35]. Interestingly, however, up to 31 % of pediatric patients with achalasia may demonstrate variable LES resting pressures, which fluctuate from between normal and abnormally elevated. In addition, normal relaxation of the LES can be seen in response to wet swallows in some pediatric patients [35]. This is contrary to traditional perceptions that achalasia is consistently associated

with insufficient or absent LES relaxation [36]. As a consequence, absence of these features does not definitively rule out a diagnosis of achalasia. Although LES function parameters do not seem to vary with the patient's age at diagnosis, those with longer symptom duration may demonstrate more consistently abnormal LES behaviour [35]. Prior to high resolution manometry (HRM) availability in children, manometry was infrequently used due to poor tolerance and large catheter size, often requiring sedation and limiting interpretation [37]. HRM now allows unsedated studies in the majority of infants and children and experts demonstrate moderate reliability using the Chicago Classification in diagnosing children with achalasia [37, 38].

Endoscopy

Upper endoscopy is a useful adjunct and should be used to rule out other potential etiologies of dysphagia and feeding intolerance. These include eosinophilic esophagitis, malignancy, candidal infection, mechanical strictures or rings, and sequelae of advanced GERD [5, 35]. In many institutions, endoscopy with esophageal biopsy is included routinely in the workup of achalasia [32].

Other Diagnostic Modalities

There are case reports of other imaging modalities including gastroesophageal radionuclide studies [39, 40] and ultrasonography [41] for both diagnosis and treatment monitoring in children with achalasia, and may be useful adjuncts when specific considerations limit the use of other diagnostic modalities.

Therapy and Outcomes

In the pediatric population, there are currently no definitive guidelines for treating achalasia. The general principles of treatment are similar to those utilized in adults, although responses to specific interventions differ somewhat.

Medical/Pharmacologic

While not considered definitive therapy for achalasia in children, certain pharmacologic agents may be considered for symptom relief either as a bridge to further treatment, or in patients who have strong medical contraindications to balloon dilation or esophagomyotomy. Calcium channel blockers such as nifedipine have been used in adults, but there is minimal study around their use in children. One series of four adolescent patients treated with nifedipine demonstrated significant symptom improvement and increased LES relaxation [42], while other sources suggest that side effects of these drugs are poorly tolerated in this population with increasing doses and they are not recommended as first line treatment [43].

Endoscopic Botox Injection

Botulinum toxin inhibits acetylcholine release by binding presynaptic cholinergic nerve terminals, resulting in smooth muscle relaxation. When injected endoscopically into the LES, Botox has demonstrated efficacy in relieving symptoms of achalasia in both the adult and pediatric populations [44-46]. The procedure is fairly easy to perform, with very few complications [46]. In the pediatric population, an initial response rate of approximately 80 % has been shown with a mean duration effect of 4-6 months [44, 46]. Unfortunately, only a small proportion of pediatric patients respond to a single injection without need for any further medical or surgical intervention [46], suggesting that while botulinum injection is an effective intervention for symptom relief, dilation or myotomy should still be considered for definitive treatment.

Endoscopic Balloon Dilation

Balloon dilatation (BD) with resultant disruption of the LES has been well established as an effective intervention for achalasia in adults. Several retrospective case series report on the use of this intervention in children with long-term symptom relief in 65-80 % of patients followed for 2-8 years [47-50]. Possible complications include gastroesophageal reflux, prolonged retrosternal or epigastric pain and perforation. The risk of perforation in adult literature is less than 5 % in most series [36, 51] and one series of 50 pediatric procedures demonstrated similar results, with a perforation rate of 6 % [52]. While successful balloon dilations have been done for achalasia patients as young as 7 weeks, many authors recommend avoiding balloon dilation in younger children (under 5-9 years) due to technical limitations and perceived increased risk of complications [48, 53, 54]. A recent systematic review comparing balloon dilation to Heller myotomy concluded that there is insufficient evidence to recommend an optimal treatment algorithm, but that both adult and pediatric studies suggest poorer outcomes from balloon dilation in younger patients [6].

Despite the need for repeat intervention, balloon dilation has been demonstrated to be a cost effective, relatively low risk procedure for achalasia treatment [32, 34]. If this treatment modality is chosen, those who fail to improve with more than one dilation over the course of a year should be considered for surgical myotomy [7].

Surgical Myotomy

Cardiomyotomy, first described by Heller, involves division of the LES, from the esophageal wall, with extension interiorly over the first 2 cm of the gastric cardia [43]. Although originally performed through a laparotomy, open myotomy has largely been replaced by the Laparoscopic Heller Myotomy (LHM) with an antireflux procedure. As with many other laparoscopic procedures, a minimally invasive approach offers numerous benefits including improved cosmesis, decreased post operative pain, shorter hospital stay, and faster return to activity [55, 56]. At present, surgery is considered the most definitive treatment for achalasia [32, 57] with longer symptom resolution than balloon dilation in multiple pediatric studies [7, 34, 53, 54]. Potential complications include immediate or delayed perforations of the esophageal mucosa, recurrent dysphagia, GERD, and incomplete myotomy necessitating balloon dilation, or repeat surgical intervention [32, 57]. To limit complications, some centers performing pediatric laparoscopic Heller myotomy also advocate for use of intraoperative manometry or endoscopy to avoid incomplete myotomy and possibly aid intraoperative identification of perforation [58, 59].

The need for antireflux procedure in combination with myotomy is somewhat controversial. Although a single series of patients treated with LHM alone did not demonstrate significant reflux post-operatively [60], the majority of pediatric studies suggest LHM with fundoplication is superior to LHM alone for prevention of postoperative GERD [8, 32]. While the type of antireflux procedure has not been examined in depth in the pediatric population, randomized studies in adults have demonstrated significantly more post-operative dysphagia in achalasia patients who received a Nissen fundoplication when compared to those receiving a Dor [57]. At present, most pediatric studies have utilized the Dor fundoplication [7, 8, 32, 61].

Per Oral Endoscopic Myotomy (POEM)

Although the Heller myotomy is still considered the surgical treatment of choice for children with Achalasia, more evidence is gathering to support the use of POEM in this population. The technique of POEM has been described previously [62, 63] and consists of a longitudinal myotomy of the circular esophageal musculature once a submucosal tunnel using carbon dioxide insufflation and coagulation has been created. A recent retrospective study of eighteen pediatric patients with achalasia examined outcomes of LHM with Dor fundoplication compared with the POEM technique, and demonstrated comparable symptom improvement in both groups, with similar times to feeding and discharge from hospital [62].

Current concerns surrounding the use of POEM include the inability to perform an antireflux procedure, potential increased risk of iatrogenic GERD [64]. Technical factors related to patient weight/size in addition to the learning curve of the endoscopist also deserve more attention and consideration as utilization of this procedure increases [62]. While more investigation into long-term outcomes in larger numbers is certainly needed, early results suggest POEM may be a promising option for the treatment of pediatric achalasia in coming years.

In summary, achalasia is rare in pediatrics and the majority of diagnostic and therapeutic considerations are similar to adults. Special considerations in children include identification of achalasia in the setting of genetic syndromes and difficulties making the diagnosis due to symptoms that mimic more common childhood illnesses. Special diagnostic and treatment concerns also relate to the size of younger patients affecting manometry and endoscopic procedures, and the need for longer-term efficacy of symptom palliation in a child with his or her life ahead of them. Further studies are needed to determine the ideal treatment option and develop a cure for children and adults with this disease.

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