Pediatr Surg Int (2012) 28:1229–1233
DOI 10.1007/s00383-012-3186-3

CASE REPORT

Familial achalasia in children

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Accepted: 1 October 2012 / Published online: 18 October 2012

Abstract Achalasia is rare in the pediatric age group and in most cases it is idiopathic with no family history. Familial achalasia is very rare. This report describes two families with achalasia: in one, six children were affected while in the other a brother and a sister had Allgrove's syndrome (triple-A syndrome consisting of achalasia, adrenal insufficiency, and alacrima). Familial achalasia suggests that it is hereditary and may be transmitted as an autosomal recessive trait. The management of achalasia in children is still controversial. With the recent advances in minimal invasive surgery, laparoscopic Heller's myotomy is the procedure of choice in the management of achalasia in children.

Keywords Achalasia · Children · Familial · Hereditary · Heller's myotomy

Introduction

Achalasia is a primary esophageal disorder characterized by loss of lower esophageal sphincter relaxation and loss of esophageal peristalsis. This leads to functional obstruction of the distal esophagus. The exact etiology of achalasia is not known and several factors including autoimmune, infectious, environmental, and genetic have been suggested as possible etiological factors but in the majority achalasia is idiopathic [1–6]. The recent discovery of positive association of class II HLA antigen DQwI suggests an immunogenic etiology for achalasia [7, 8]. The genetic etiology of achalasia is suggested by the familial occurrence where several members of the same family can be affected [9–11]. Add to this a wide variety of syndromes associated with achalasia. These include Sjogren's syndrome, Allgrove's syndrome (triple-A syndrome consisting of achalasia, adrenal insufficiency, and alacrima), Rozychi's syndrome (deafness, typical leucoderma, muscle wasting, and achalasia), Down's syndrome, and Pierre-Robin syndrome [12–15]. Reports of isolated familial achalasia are rare and represent less than 1 % of all patients with achalasia [16–18]. This report describes two families with achalasia: in one, six children were affected while in the other a brother and a sister had Allgrove's syndrome.

Case no. 1

A 9-month-old female was admitted to our hospital with vomiting undigested food of 3 months duration and recurrent chest infection as well as failure to thrive. Clinically, there were no abnormalities apart from failure to thrive (weight 6.6 kg). There was a strong family history of achalasia. There were nine children in the family; six of them had achalasia (Fig. 1). There were four boys and two girls. In all, the symptoms started around the age of 6 months and the diagnosis was confirmed by barium swallow. Molecular genetic studies were done on the members of the family and showed normal results and no

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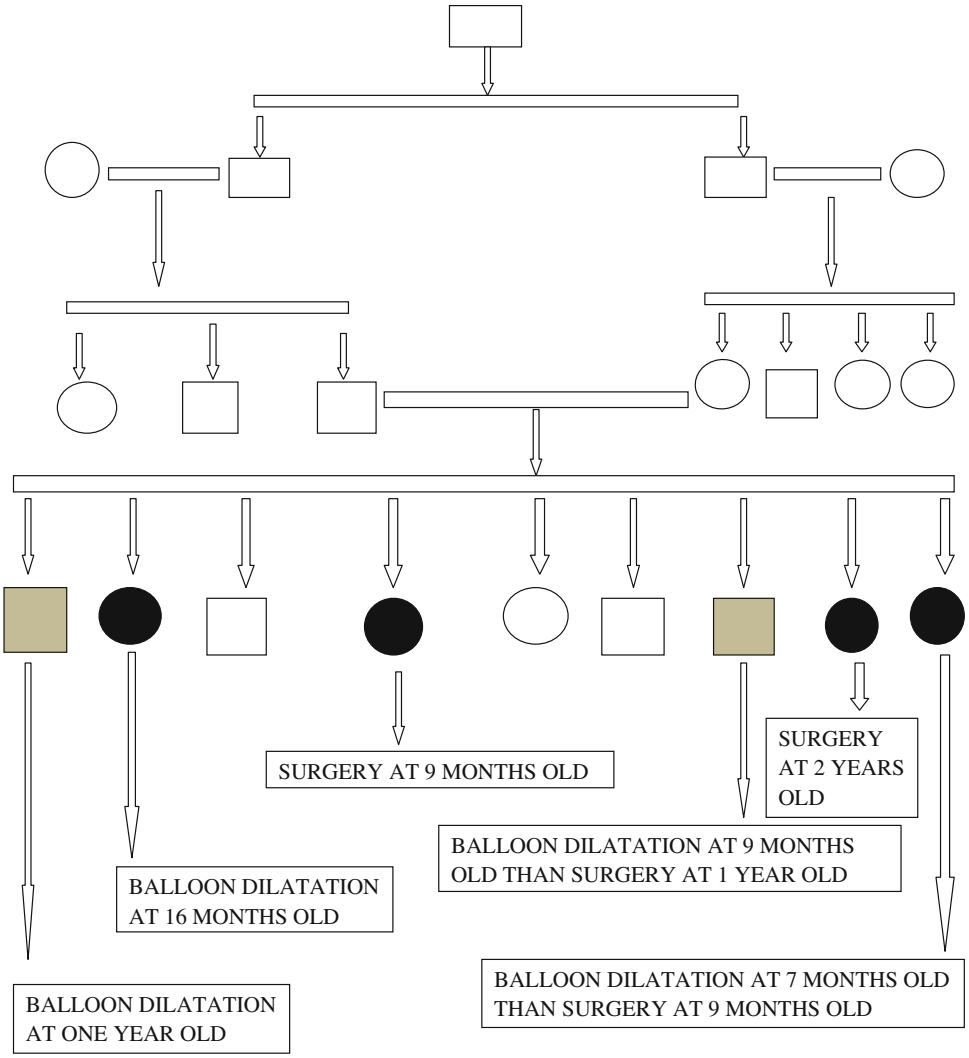

Fig. 1 Family pedigree showing six children affected with achalasia. Note the early age of onset

DNA variants that could contribute to the phenotype were identified in the AAAS gene. The result does not exclude AAAS variants as variants outside of the analyzed region or variants not detectable by sequencing might be present. The age and different modalities of treatment are shown in Fig. 1. Two had balloon dilatation only and responded well, two had open Heller's esophagomyotomy with Thal antireflux procedure and did well. The remaining two patients had balloon dilatation but did not show improvement and had surgery. One of them had open Heller's esophagomyotomy with Thal antireflux procedure while the other one had laparoscopic Heller's myotomy with Dor antireflux procedure and are doing well.

Case no. 2

A 2.5-year-old male child was referred to our hospital with repeated attacks of vomiting since the age of 6 months. His birth weight was 2.5 kg. His weight at the age of 2 years was 10.5 kg and at the age of 2.5 years was 9.7 kg. Clinically, he was thin built with dry eyes (alacrima). His electrolytes were normal and his ACTH level was 61.3 pg/ml (normal 0–46 pg/ml). His cortisol was 0.3 μg/dl and 60 min after ACTH stimulation was 12.2 μg/dl (normal 6.2–19.4 μg/dl). On two occasions, he was admitted to the hospital because of hypoglycemic convulsions and several times for exacerbations of bronchial asthma. His barium swallow showed features of achalasia (Fig. 2). He was diagnosed as Allgrove's syndrome and underwent esophageal balloon dilatation with only transient improvement. Subsequently, he underwent Robotic-assisted Heller's myotomy using the DaVinci Robotic system, with marked improvement and increase in his weight. Currently, he is on hydrocortisone treatment. He had a follow-up barium swallow which showed normal emptying of the esophagus with no evidence of gastroesophageal reflux. His sister, a 2-year-old female, was referred to our hospital with repeated attacks of vomiting; she also had alacrima. Clinically, she was normal looking with dry eyes. Barium swallow showed features of achalasia. She did not show clinical or

Fig. 2 Barium swallow showing features of achalasia. Note the bird's peak sign

biochemical features of adrenal insufficiency at this stage. She underwent Robotic-assisted Heller's myotomy using the Da Vinci Robotic system. Post operatively, she had a good recovery and her symptoms improved markedly with increase in her weight.

Discussion

Achalasia is a primary esophageal motility disorder characterized by failure of lower esophageal sphincter to relax and the absence of esophageal peristalsis. These abnormalities cause a functional obstruction at the gastroesophageal junction. The incidence of achalasia is approximately 0.8–1 per 100,000 people per year. In the pediatric age group, achalasia is rare with fewer than 5 % of cases occur in children [19, 20].

The etiology of achalasia is still unknown and in the majority it is idiopathic. Several factors have been incriminated in the pathogenesis of achalasia. These include neuronal degeneration (degeneration of Auerbach's plexus), viral infection, genetic inheritance, and autoimmune disease [1–6]. The genetic etiology of achalasia is interesting. This is especially so in the pediatric age group where in certain cases achalasia is congenital and somewhat different from the adult type [18]. This is supported by several factors including: (1) the occurrence of achalasia in children prior to the age of 6 month, (2) the existence of familial cases where several members of the same family are affected, (3) the occurrence of achalasia in monozygotic twins, (4) the association of achalasia with certain syndromes like Allgrove's syndrome, familial dysautonomia, glucocorticoid insufficiency, Rozycki's syndrome and Pierre-Robin syndrome [9–19]. In these settings, it has been suggested that achalasia may be transmitted as an autosomal recessive trait. Zimmerman and Rozenzweig [11] reported 66 cases of familial achalasia. In our first case, six members of the same family were affected by achalasia and in all their symptoms started early before the age of 6 months. This familial occurrence of achalasia is supported by a number of reports from around the world where several members of the same family are affected. Our second case is a brother and a sister with Allgrove's syndrome. Allgrove's syndrome, the so-called triple-A syndrome, is a rare and an interesting condition inherited as an autosomal recessive disorder. The locus for the abnormal gene was described on chromosome 12q13 which is called ALADIN. However, the pathophysiology of achalasia in Allgrove's syndrome remains obscure. In 1978, Allogrove et al. [13] described two unrelated pairs of siblings with glucocorticoid deficiency and achalasia of the esophagus. Three of them also had defective tears production. This was called 3A syndrome (Adrenal insufficiency, Achalasia, Alacrima). Subsequently, several authors described autonomic disturbances associated with the original Allgrove's syndrome, hence the name 4A syndrome (Adrenal insufficiency, Achalasia, Alacrima, Autonomic disturbances) [21, 22].

The management of achalasia in the pediatric age group is still controversial. One contributing factor is the limited number of pediatric patients with achalasia [19]. There are several modalities of treatment for achalasia. These include esophageal dilatation (hydrostatic or pneumatic), pharmacological therapy (botulinum toxin injection and nifedipine), and operative (open or laparoscopic Heller's myotomy) [23–28]. In the pediatric age group botulinum toxin injection is not recommended and the results of esophageal dilatation whether hydrostatic or pneumatic are not clear [20, 24]. Esophageal dilatation will ameliorate the symptoms but this may be temporary. This was the case in three of our patients who had hydrostatic balloon esophageal dilatation. There was a definite response to dilatation but this was only temporary. Only two of our patients responded well to esophageal dilatation. This pushed us towards early surgical Heller's myotomy for the remaining patients. Heller's myotomy although does not treat the esophageal dysmotility, it does significantly improves symptoms of achalasia. Three of our patients had open Heller's myotomy and were treated initially. With the recent advances in minimal invasive techniques, the two

patients with Allgrove's syndrome underwent Robotic-assisted Heller's myotomy and one had laparoscopic Heller's myotomy. Following surgery, there was a definite improvement in their symptoms as well as an increase in their weight. We like others advocate Heller's myotomy as the procedure of choice in the management of achalasia in children [18, 20]. This is specially so in the era of minimal invasive surgery. Following Heller's myotomy, there is a definite risk of developing gastroesophageal reflux, and to reduce this, an antireflux procedure is advocated without impairing esophageal or gastric emptying [26, 27]. This was the case in our patients who underwent Heller's myotomy except the two with Allgrove's syndrome. In the patients with Allgrove's syndrome, we elected not to add an anti-reflux procedure because of the fear of post-operative dysphagia as a result of the associated autonomic neuropathy. To overcome this and reduce the chance of developing post-operative gastroesophageal reflux, we left the retroesophageal space undisturbed. Persistent dysphagia in these patients, however, should be investigated to rule out incomplete myotomy or a too tight antireflux procedure.

In conclusion, achalasia is rare in children and must be considered in infants and children presenting with dysphagia. In most cases there is no family history, and it occurs as an isolated entity of unknown etiology. Familial achalasia is extremely rare and suggests a genetic predisposition to achalasia which is transmitted as an autosomal recessive inheritance. Its association with other syndromes such as Allgrove's syndrome should stimulate physicians caring for these patients to investigate them, as early diagnosis is important to obviate further complications. The importance of a good family history in this regard must be stressed as this may help to identify affected siblings and other family members. Although pneumatic dilation is the most common first-line therapy for the treatment of achalasia, Heller's myotomy is the procedure of choice in the management of achalasia in children. This is specially so in the era of minimal invasive surgery. An anti-reflux procedure should be added to overcome the risk of gastroesophageal reflux developing in these patients postoperatively. This however may not be the case for those with Allgrove's syndrome where the associated autonomic neuropathy in these patients precludes adding an anti-reflux procedure which may lead to post-operative dysphagia.

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