




Familial achalasia isolated or syndromic: about 18 families

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Abstract

Aim: Familial achalasia (FA) is a very rare condition. This work aims to evaluate its prevalence, characterize its clinical profile in a large series, and assess the efficacy and safety of pneumatic dilation (PD) in this context.

Methods: A total of 817 patients with achalasia were collected over a period of 20 years (1990–2010). All cases of FA: isolated or associated to Allgrove syndrome, were looked for in both parents and siblings.

Results: In this study, 18 families with FA were identified $n = 41$ patients (5%). Two members were affected in each family, in 14 families, three members per family in three others, and for the remaining family 04 members. All cases of achalasia were observed in siblings and parent to child transmission was unfound. Achalasia was associated to Allgrove syndrome in 15 families. It was isolated in 3 families. Consanguinity was found in 89% of patients, and death at a young age in the siblings was recorded in 27% of cases. Achalasia was present before the age of 5 years in 75% of cases. There was no difference between the two groups for age, age at onset, sex and the presence of the cardinal signs of achalasia. A total of 102 dilations were performed. Only one session in 31% of cases, two in 38%, three in 17% and more than three sessions in 14%. The long-term success rate of PD was low.

Conclusions: FA manifests almost exclusively in childhood. It is rarely isolated; most often falls under Allgrove syndrome. Alacrima is the earliest sign that should lead to the diagnosis. The long-term success rate of PD is rather low. This requires recourse to multiple sessions of PD or Heller's cardiomyotomy which may be the best initial approach.

Keywords

Familial, isolated, achalasia, Allgrove syndrome, 3A syndrome, pneumatic dilation, Heller's cardiomyotomy



Introduction

Achalasia is a primary esophageal motility disorder characterized by esophageal aperistalsis and failure of the lower esophageal sphincter (LES) to relax with swallowing, secondary to a degeneration of the myenteric plexus [1, 2]. Its etiology remains, to date, unknown. However, the existence of family cases—most often falling under Allgrove syndrome—suggests the existence of genetic factors predisposing to this condition [3, 4]. The genetic etiology of achalasia is suggested by the familial occurrence where several members of the same family can be affected [5, 6]. Achalasia is rare in children. In most cases, it is idiopathic with no family history. It occurs exceptionally in siblings. To our knowledge, only 33 cases of familial childhood achalasia were collected in the literature till 1987. Familial achalasia (FA) is a very rare condition [7]. Very few studies are available and tackle usually isolated cases [8]. Its management has not been established: pneumatic dilation (PD) or Heller's cardiomyotomy. This work aims to evaluate the prevalence of FA, study its clinical profile in a large series and assess the efficacy and safety of PD in this context.

Materials and methods

In this prospective study, 817 patients with achalasia were enrolled over a period of 20 years (1990–2010), 425 were females (F), 392 were males (M), mean age: 38.3 years \pm 18.7 years (3 months–86 years), children presented 8% of cases. Achalasia was diagnosed on clinical, endoscopic, radiological and manometric arguments. All patients underwent a standardized symptoms questionnaire, an upper endoscopy, a barium esophagogram and esophageal manometry. Achalasia definitive diagnosis was made according to manometric criteria: a total aperistalsis associated or not to an increased LES tone (> 34 mmHg) and/or a LES failure to relax ($< 80\%$ of the basal pressure). FA isolated or associated to Allgrove syndrome was systematically checked in both parents and siblings. Its diagnosis was established when at least two members of one family had achalasia, whether it was isolated (sporadic achalasia) or fallen under Allgrove syndrome (syndromic achalasia). Allgrove syndrome is a rare autosomal recessive disorder characterized by alacrima, achalasia, adrenal insufficiency and neurological abnormalities. Rarely reported in adult patients, it is usually present during the first decade of life. Recent studies have identified mutations in the triple A syndrome gene (*AAAS*), a candidate gene on chromosome 12q13 (16 exons). The most common mutations are missenses or frameshift, predicting a truncated presumably non-functional protein called Alacrima Achalasia aDrenal insufficiency Neurologic disorder (*ALADIN*). The *IVS14* and *EVS9* are the most common mutations. Its diagnosis was made when at least two out of the 3 following signs were present: alacrima, achalasia, adrenal insufficiency. It was classified as 2A in case of absence of adrenal insufficiency, 3A when the 3 signs were present and 4A in case of their association with neurological abnormalities.

Graded PD with Witzel dilator and/or Rigiflex balloon was performed for all patients. It was carried out every week until remission. After complete dilation, the patients were controlled after 1 month, 6 months and then yearly. Clinical results were evaluated according to Vantrappen classification and/or Eckardt score. If during the follow up symptoms relapsed, patients underwent subsequent sessions of PD (1 session to 3 sessions yearly) or Heller's cardiomyotomy.

Results

Clinical outcomes

Among the 817 patients included in our study, 18 families with 41 patients (5%) were identified (mean age: 16 years \pm 8.2 years, extremes: 4–37). In 14 families, 2 members were affected in each, in three others, 3 members per family and for the remaining family, 4 members were affected. Achalasia was isolated [group A: classic achalasia or isolated familial achalasia (IFA)] in 3 families (n : 7, F: 4, M: 3; mean age: 14.6 \pm 8). It was associated to Allgrove syndrome [group B: Allgrove familial achalasia (AFA)] in 15 families (n : 34, F: 20, M: 14; mean age: 16.8 \pm 8). 3A syndrome (alacrima, achalasia, adrenal insufficiency) was observed in 67%, 2A syndrome (alacrima, achalasia) in 23.6% and 4A syndrome (alacrima, achalasia, adrenal

insufficiency, autonomic neuropathy) in 8.8%. Achalasia was observed in siblings (transversal transmission). Parent to child transmission (vertical transmission) was not found. Consanguinity was noticed in both groups: 89% of patients (AFA: 73.8%/IFA: 15.2%). It was 3 times more frequent with Allgrove syndrome. Alacrima was constant and present at birth in all cases of Allgrove syndrome. Achalasia was present before the age of 5 years in 75% of cases. There was no difference between the two groups for age, age at onset, sex and the presence of the cardinal signs of achalasia (dysphagia, regurgitations, weight loss and pulmonary symptoms). However, short stature, mental retardation and alacrima were exclusively present in AFA group in 20%, 35% and 100% of cases respectively. Death at a young age among siblings and death during follow up were exclusively associated to AFA group, too in 27% and 6% of cases, probably due to adrenal insufficiency.

PD outcomes

A total of 102 dilations were performed (mean: 2.5 ± 1.5 per patient). Only one session in 31% of cases, two in 38%, three in 17% and more than three sessions in 14%. PD was well tolerated in all patients, no perforation occurred in this study. Immediate success (short term) was obtained in 28 patients (68%) and failures in 32%. However, after a median follow up of 5.3 years, the success rate dropped to 24% and failures raised up to 76%. There was no difference between the two groups for PD results regarding short or long term remission. Regarding treatment, 11 patients underwent Heller's cardiomyotomy with success in 67%, 10 others took isosorbide dinitrate and improved in 60% of cases and 20 patients are still treated by iterative PD (1 session/year to 3 sessions/year).

Discussion

FA is a very rare disease [7]. Its prevalence is unknown, and only scattered family and case reports exist in the literature [9]. This prospective work focused on a large series of 41 patients with FA among the 817 patients with achalasia included in our study. These patients came from the 48 provinces of Algeria as our department is a reference center for managing this condition. This is a homogenous and representative sample of Algerian population, from which it was possible to estimate, for a period of 20 years, the relative prevalence of this disease to the whole cases of achalasia in Algeria and to study its clinical and para clinical features. Our work has shown that its relative prevalence was estimated to be 0.05 (5 cases of FA/100 cases of achalasia) CI 95%: (0.035, 0.065). FA is more frequent in children, Zimmerman and Rosensweig [10] have commented that approximately two thirds of reported cases of FA have occurred in children under the age of 15 years, which is similar to our result ($n = 31$, 75% of cases). There is a preponderance of horizontal transmission in FA [11]. It suggests a genetic predisposition that is transmitted as an autosomal recessive trait [8]. Westley and colleagues [12] believed that the lack of evidence of vertical transmission and the occurrence of achalasia in children of both sexes and in multiple members of an extended family constituted strong evidence that a recessive gene was responsible for infantile achalasia [9]. Thus, vertical transmission may well exist, but its documentation is difficult (Table 1) [11].

Table 1. Family occurrence of achalasia with vertical transmission

References	Affected family members	Sex (M/F)	Age at onset (yr)
Evsytina et al. [13]	Mother/daughter	F/F	23/25
Raj and Rajan [14]	Mother/son	F/M	75/48
Zimmermann and Rosensweig et al [10]	Son/father	M/M	36/72
Chawla et al. [15]	Mother/son	F/M	72/45
Mackler and Schneider [16]	Son/father	M/M	37/63
Kilpatrick and Milles [17]	Mother/daughter	F/F	59/46

yr: year

Note. Adapted from "Family occurrence of achalasia and diffuse spasm of the oesophagus," by Frieling T, Berges W, Borchard F, Lübke HJ, Enck P, Wienbeck M. Gut. 1988;29:1595–602. <https://gut.bmj.com/content/29/11/1595>. CC BY-NC.

Allgrove syndrome is a very rare genetic autosomal recessive disorder. Its occurrence is favored by consanguineous marriages. The *AAAS* gene responsible for this disease is carried by the long arm of chromosome 12 (12q13) and contains 16 exons. Mutations of this gene that were currently implicated are *IVS14*, the most common mutation, and *EVS9* [18–19]. Alacrima was constant and present at birth in all cases of Allgrove syndrome this should lead to the diagnosis. Achalasia is the most common disorder seen after alacrima. Adrenal insufficiency is not constant and neurological abnormalities can exist without it [20].

Despite its rarity, Allgrove syndrome must be known by the internist who may have to make the diagnosis in an adult patient suffering from asthenia, melanoderma, and adrenal insufficiency or a predominantly motor peripheral axonal neuropathy which may first suggest Charcot-Marie-Tooth disease or a motor neuron disease. The importance of its multidisciplinary management is certain, as the diffusion of its knowledge in the medical community, because of its prognosis which is hampered by neuropathic and adrenal damage.

In our study, two groups of FA were identified. Group A: IFA in 3 families ($n: 7$, F: 4, M: 3; mean age: 14.6 ± 8). Group B: AFA in 15 families ($n: 34$, F: 20, M: 14; mean age: 16.8 ± 8). These results show a high rate of AFA. This is most probably related to the widespread tradition of consanguineous marriage in Algeria. Reports of IFA are very rare and represent less than 1% of all patients with achalasia [21]. So far, no study has compared AFA and IFA. Based on reported cases and our results, we can notice the differences summarised in (Table 2). Most of our FA patients were children. This explains the low long-term success of PD dilation because it is characterized as a temporizing, non-definitive procedure for this age [9, 22], and surgical management may be the best initial approach [7, 9].

Table 2. Comparison between IFA and AFA

Parameters	AFA	IFA
Etiology	Mutations <i>AAAS</i> 12q13	Multifactorial Genetic? Environment?
Disease	Multisystemic	Esophagus
Frequency	5 times	1 time
Consanguinity	73.2%	15.2%
Disease transmission	Horizontal only siblings	Horizontal/vertical siblings
Prognosis	Autonomic abnormalities Adrenal insufficiency	Good
PD	Low long-term remission	

?: not proven as an etiological factor (remains hypothetical)

Conclusion

FA is almost exclusively infantile. It is rarely isolated and most often falls under Allgrove syndrome. It almost exclusively affects siblings. Alacrima is the earliest sign that should lead to the diagnosis of the Allgrove syndrome. The long-term success rate of PD is rather low, resulting in permanent successful treatment in less than a quarter of patients which requires recourse to multiple sessions of PD or Heller's cardiomyotomy which may be the best initial approach.

Abbreviations

AAAS: triple A syndrome gene

AFA: Allgrove familial achalasia

F: females

FA: familial achalasia

IFA: isolated familial achalasia

LES: lower esophageal sphincter

M: males

PD: pneumatic dilation

Declarations

Author contributions

AT: Conceptualization, Resources, Data curation, Formal analysis, Supervision, Funding acquisition, Validation, Investigation, Visualization, Methodology, Writing—original draft, Project administration, Writing—review & editing. FB: Resources, Formal analysis, Investigation, Visualization, Methodology, Writing—review & editing. MEAB: Resources, Investigation. ML: Resources, Investigation. NO: Resources, Investigation.

Conflicts of interest

The authors declare that they have no conflicts of interest.

Ethical approval

An ethical approval was obtained and the protocol of the study was approved by the hospital ethical committee.

Consent to participate

Informed consent to participate in the study was obtained from all participants.

Consent to publication

Informed consent to publication was obtained from relevant participants.

Availability of data and materials

The datasets of this study can be found in Tebaibia's data base, and can be shared on demand.

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