Allgrove syndrome and motor neuron disease

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Abstract

Allgrove or triple A syndrome (AS or AAA) is a rare autosomal recessive syndrome with variable phenotype due to mutations in *AAAS* gene which encodes a protein called ALADIN. Generally, it's characterized by of adrenal insufficiency in consequence of adrenocorticotropic hormone (ACTH) resistance, besides of achalasia, and alacrimia. Neurologic features are varied and have been the subject of several case reports and reviews. A few cases of Allgrove syndrome with motor neuron disease have been already described. A 25-year-old white man, at the age of four, presented slowly progressive distal amyotrophy and weakness, autonomic dysfunction, dysphagia and lack of tears. He suffered later of orthostatic hypotension and erectile dysfunction. He presented distal amytrophy in four limbs, tongue myofasiculations, alacrimia, hoarseness and dysphagia due to achalasia. The ENMG showed generalized denervation with normal conduction velocities. Genetic testing revealed 2 known pathogenic variants in the *AAAS* gene (c.938T>C and c.1144_1147delTCTG). Our case presented a distal spinal amyotrophy with slow evolution and symptoms and signs of AS with a mutation in AAAS gen. Some cases of motor neuron disease, as ours, may be due to AAS. Early diagnosis is extremely important for symptomatic treatment.

Introduction

Allgrove *et al.* (1978) described two unrelated pairs of siblings with glucocorticoid deficiency and achalasia.[1] The latter condition involved delayed passage of food into the stomach and dilation of the thoracic oesophagus. Three of these individuals also had defective tear production, leading the authors to speculate that the combination of adrenal deficiency, achalasia, and alacrimia represented an inherited familial disorder. The authors also referred to the prior publications of Kelch *et al.* (1972) as well as Counahan and West (1974),[2,3] who reported patients with hereditary adrenal unresponsiveness to adrenocorticotropic hormone (ACTH). Allgrove pointed out that these patients developed achalasia and suggested that all of the patients shared a common syndrome. It is a rare disease and inherited as an autosomal recessive trait.[1] It is caused by the mutation(s) in the AAAS gene, present on chromosome 12q13 and that changes ALADIN protein, generating signals like achalasia, alacrimia, neurologic disorder, adrenal insufficiency.[4,5] The exact function of this protein is still not known. The protean presentation of this disorder is related to dysfunction of nuclear pore complexes (NPC), despite apparently normal structure of these large multiprotein assemblies.[6] It's prevalence is of 1 per 1,000,000 individuals.[7] Neurologic features are varied and have been the subject of several case reports and reviews. The most commonly described abnormal features of the neurologic examination are hyperreflexia, dysarthria, hypernasal speech with palatopharyngeal incompetence, and ataxia.[8] A few cases of Allgrove syndrome with motor neuron disease have been already described.[9] The main aim of our work is to report a case of *AAA* syndrome that presents a form of a distal spinal muscle atrophy.

Case Report

A 25-year-old white man, the only child of non-consanguineous parents, student, reported that with four years old he had noticed mild weakness and amyotrophy of hands and feet. He said never presenting tears and five years ago he referred change in timbre of his voice as well as difficulty in speech and deglutition. The neurologic examination showed atrophy and paresis (MRC 4) of the intrinsic of the hands and orsal flexor of feet, tongue fasciculations and atrophy (Figure 1). The deep reflexes were abolished in the lower limbs and normal in upper limbs. Superficial and deep sensitivity are normal. The tongue was atrophic with fasciculation. There were orthostatic hypotension and increased heart rate. Electroneuromyography showed generalized denervation with normal sensory and motor conduction. Alacrimia was reported by his mother and later confirmedin Schimmer (below 1 mm) test. The biomicroscopy tests with fluoresce in and green his amy revealed: keratoconjunctivitis sicca, keratitis and accumulation of mucus on the corneal surface without impregnation by green his amy and absence of tears. Oesophageal manometry was characterized by normal basal pressure in lower sphincter with incomplete relaxation, absence of peristalsis in swallowing in the oesophageal body (achalasia). Gastric-oesophageal junction showed diaphragmatic clamping with slight resistance to the passage of the apparatus in the presentation.The blood and the endocrine tests were normal: cortisol, 13.8 mmg/dL; FSH, 3.64 mmUI/mL; LH 3.8 mmUI/mL; Testosterone, 593.8 nanogram/dL; ACTH, 1.5 picogram/mL. The patient underwent whole exome sequencing and two known pathogenic variants in the *AAAS* gene were found. The first c.938T>C (HGMD: CM023869) is a missense mutation that

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leads replaces the aminoacid Alanine for Valine in the residue 313 of the protein. The second variant c.1144_1147delTCTG (HGMD: CD024030) is a small deletion that disrupts the open reading frame and results in a premature stop codon (p. S382Rfs*33) (Figure 2).

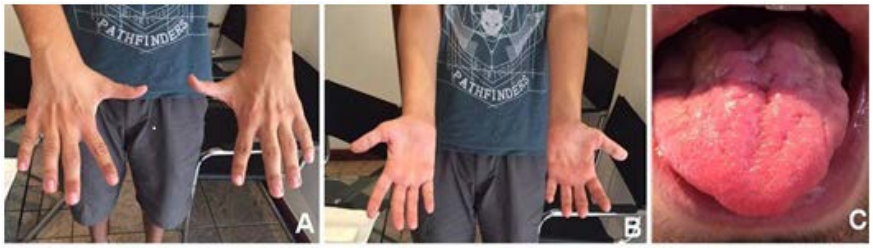

Figure 1. A, B) Symmetrical amyotrophy of interosseous, tenars and hipotenars muscles in both hands. C) Atrophy and myofasciculations of the tongue.

Discussion

The prevalence of AS is unknown, mainly because its description in the world literature is limited to case reports. AS is an autosomal recessive congenital disease. AS does not appear to be age, ethnicity or gender specific but varies widely in severity, with some patients developing no symptomatology and others suffering a fatal outcome. Paediatric patients with AS often present with the classic triad of triad of symptoms, while patients with the late onset or adult onset condition exhibit symptoms that involve the nervous system.[10,11] Vishnu *et al*. (2014) suggested that neurological symptoms may manifest in certain subgroups of patients with a less severe and chronic course of the disease.[9] In some cases, as in ours, the AS may appears earlier on.[12]

AAAS patients commonly show associ-

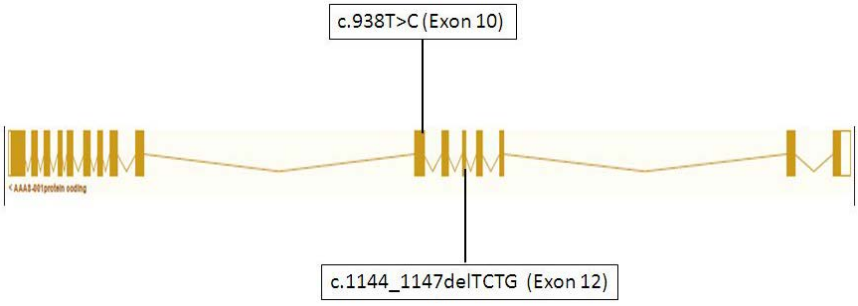

Figure 2. Structure of the *AAAS* gene (transcript ENST00000209873) showing the 16 coding exons and the location of the 2 identified variants.

Table 1. Cases reported in the literature of Allgrove syndrome with motor neuron disease.

Author	Case (year, sex)	Year of first sympton	General manifestation	Neurologic manifestation	Genetic mutation
Houlden *et al.* (2002) [15]	36, male	Slowly progressive achalasia, NI	AC, AL	DSA, BP, SP, small and furrowed tongue	Heterozygous mutations G15K, c.1186InsC
Nakamura *et al.* (2010) [27]	40, male	NI, AC	AC,AL,ON, AD	DSA, SMN	Homozygous for a missense mutation, p.R155H,
Ledesma *et al.* (2013) [25]	19, male	10, vomiting	AL, AC and gastroesophageal reflux	SMN, AD, SP	Two mutations: p.Tyr19Cys, IVS14 + 1G- A.
Bizzarri *et al.* (2013) [4]	13, male	4 years. Episodes of hypotonia, hypoglycemia and hypothermia	Recurrent vomiting, failure to thrive and progressive skin pigmentation,gastro-esophageal reflux; hypoglycemia and hypothermia.	Dysphagia, DSA, SMN, syringomyelia	Homozygous missense mutation in exon 12. T > G transversion at nucleotide position 1224 resulting in a change of leucine at amino acid position 381 into arginine (Leu381Arg or L381R)
Ikeda *et al.* (2013) [28]	Six patients 54, 29, 23 female; 49, 14, 38, 60 male	12,5, 6 years female 18,13, 25 male AC, hyperpigmentation	AD, AC, AL, ON, MI	DSA	p.I4882S, p.I4882S, p.R119X, p.R194X, p.S182fsX19, p.R155H
Vishnu *et al.* (2014) [9]	22,male	22, AC	AC, AD	DSA	ND
Wenjing *et al.* (2015) [12]	Three patients: 7,4 female; 2 male	7,2 and 4 years vomiting	AL, AC, AD; vomiting hyperpigmentation	DSA (only case 1)	c.771delG mutation in exon 8 c.771delG mutation in exon 8 c.1366C>T mutation in exon 15
Misgar *et al.* (2015) [26]	18, male	8 year AL	AS; weakness, asthenia, fatigue,anorexia and progressive hyperpigmentation of skin for 6 months, AC, AL	DSA, SMN	ND

AC: achalasia; AL: alacrimia; AD: Addison disease; AD: autonomic dysfunction, BP: bulbar palsy; DSA: distal spinal amyotrophy; MI: mental impairment; MN: motor neuropathy; ND: not done; NI: not informed; ON: optic neuropathy; SMN: sensory

ated neurological abnormalities. As an example, impairment of the central, peripheral, and autonomic nervous system may be noted. Such manifestations appear at a later age when compared to other manifestations. Polyneuropathy is a common manifestation.[13] The literature also points to neurological manifestations such as mental retardation, parkinsonism, optic atrophy, amyotrophy, ataxia, dementia, dystonia, and chorea.[7] Microcephaly, short stature, dysmorphic features, palmar and plantar hyperkeratosis, osteoporosis, and a long QT syndrome, although less frequently, were also associated with AS.[14] Some cases of motor neuron disease have been described as bulbospinal syndrome, distal amyotrophy, amyotrophic lateral sclerosis, spastic paraparesis.[15-17] Alacrimia is a reduced or absent ability to secrete tears. Most people with triple A syndrome have all three of these features, although some have only two.[13,18]

Primary adrenal insufficiency is an uncommon disease which has worldwide distribution.[19] Individuals affected by AAA have adrenal insufficiency/Addison's disease due to ACTH resistance. Symptoms generally come on slowly and may include abdominal pain, weakness, and weight loss. Darkening of the skin in certain areas may also occur. The present case does not present adrenal insufficiency.[8,20] However, some patients may manifest it later on.

Achalasia is best characterized primary oesophageal motility disorder and typically presents with absent peristalsis of the esophageal body and a failure of the lower sphincter to relax upon swallowing on manometry, associated with progressively severe dysphagia, regurgitation, aspiration, chest pain, and weight loss. The current gold standard for establishing the diagnosis of achalasia is manometry. Especially in early stages, symptom evaluation, endoscopy and barium swallow lack adequate sensitivity. High-resolution manometry (HRM) is increasingly used and allows characterization of different achalasia types and differentiation from other motility disorders.[21] Our patient was diagnosed of achalasia after oesophagus manometry. Among the clinical findings presented by the patients, our case reports weight loss, dysphagia and regurgitation; all already with targeted drug treatment.

Orthostatic hypotension (OH) corresponds the abrupt drop in blood pressure during the change of lying down position to orthostatic position.[22] It can be asymptomatic or show symptoms, for example, syncope, dizziness, dyspnea, blurred vision, and headache.[23]

de Carvalho and Houlden (2002) reported that they had seen patients with the triple-A syndrome with severe neurologic involvement, including spastic tetraparesis, bulbospinal amyotrophy, and motor peripheral neuropathy.[24] They thank that in these cases, the marked amyotrophy can be part of the phenotypic neurologic spectrum in triple-A syndrome and suggested that amyotrophy be added to the eponym. However, others that have described cases of AAAS with neurological impairment, thinks that damage of the anterior horn of the spinal cord are rare.[25,26] Our patient presented a typical pattern of distal spinal muscle atrophy with tongue fasciculation with a long evolution. The ENMG showing denervation with normal sensory and motor conduction confirm our diagnosis. Such variants have already been described and are possibly associated with the clinical picture presented in the present case (Table 1).

The inheritance is autosomal recessive, and most cases of triple A have no family history. Using genetic linkage analysis in a small number of families, a locus on chromosome 12q13 was identified.[15] The triple A gene was identified at this locus and called ALADIN (alacrima, achalasia, adrenal insufficiency and neurologic disorder). Mutations in this gene were reported in families from North Africa and Europe. The majority of mutations were homozygous.[15] Mutations in the *AAAS* gene change the structure of ALADIN in different ways; however, almost all mutations prevent this protein from reaching its proper location in the nuclear envelope. The absence of ALADIN in the nuclear envelope likely disrupts the movement of molecules across this membrane. Some individuals with triple A syndrome do not have an identified mutation in the *AAAS* gene. The genetic cause of the disorder is unknown in these individuals.[27-29] The protean presentation of this disorder is related to dysfunction of nuclear pore complexes (NPC), despite apparently normal structure of these large multiprotein assemblies. AS can arise from mutations of the *ADRACALIN* (or *AAAS*) gene encoding the ALADIN protein of the NPC.[20]

After performing a genetic test, with new generation sequencing (NGS) to identify changes in the complete exome, our patient presented two pathogenic variants in heterozygosis in the *AAAS* gene; both associated with triple A syndrome. In our case the first search for medical assistance was initially due to muscular atrophy and weakness. At physical examination, other findings were identified (alacrimia, achalasia, OH) and, consequently, directed research into *AAAS*.

Conclusions

Some cases with distal spinal muscle atrophy similar to that seen in our patient may be undiagnosed. So it's necessary to ask for DNA tests to make a correct diagnostic, Although there is no treatment for this disease, hormone replacement therapy to treat adrenal insufficiency, artificial tears to improve eye irritation, reduce eye blink rate and prevent eye infections and corneal ulcers, application of a balloon to dilate the lower oesophageal sphincter and psychological assessment may be necessary to relieve to symptoms of the AS.

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