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 the AAS gene which encodes a protein called ALADIN. Generally, it’s characterized by adrenal insufficiency in consequence of adrenocorticotropic hormone (ACTH) resist ance, 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 amyotrophy in four limbs, tongue myofasciculations, 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 AAS 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 AAS gen. Some cases of motor neuron disease, as ours, may be due to AAS. Early diagnosis is extremely important for symptomatic treatment.

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

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 Couhanah 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 protein 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. The neurologic examination showed atrophy and paresis (MRC 4) of the intrinsic of the hands and oral 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 confirmed by Schimmer (below 1 mm) test. The biomicroscopy tests with fluorescein 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 mmU/mL; LH 3.8 mmU/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 (HMGD: CM023869) is a missense mutation that
leads replaces the amino acid 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).

**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. 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. In some cases, as in ours, the AS may appear earlier on.

AAAS patients commonly show associ-

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

| Author               | Case (year, sex) | Year of first symptom | 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. Episodic 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 14, 38, 60 male | 12.5, 6 years female 18, 30, male AC, hyperpigmentation | AD, AC, AL, ON, MI | DSA | p.14882S, p.14882S, p.R190X, p.R194X, p.S1826X19, p.R155H |
| Vishnu et al. (2014) [9] | 22 male          | 22, AC                | AC, AD                | DSA | ND |
| Wengjing 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; BP: bulbar palsy; DSA: distal spinal amyotrophy; ME: 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 oesophageal body and a failure of the lower oesophageal 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 neurologic 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 protein 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 the complete exome, our patient presented two pathogenic variants in the 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

Conclusions

Some cases with distal spinal muscle atrophy similar to that seen in our patient may beundiagnosed. 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.

References

1. Allgrove J, Clayden GS, Grant DB, Macaulay JC. Familial glucocorticoid deficiency with achalasia of the cardia and deficient tear production. Lancet 1978;1:1284-6.
2. Kelch RP, Kaplan SL, Biglieri EG, et al. Hereditary adrenocortical unresponsiveness to adrenocorticotropic hormone. J Pediatr 1972;81:726-36.
3. Counahan R, West R. Ocular and frontotemporal abnormalities in isolated glucocorticoid deficiency. J Pediatr 1974;85:580-1.
4. Bizzarri C, Benevento D, Terzi C, et al. Triple A (Allgrove) syndrome: an unusual association with syringomyelia. Ital J Pediatr 2013;39:1-5.
5. Sarathi V, Shah NS. Triple-A syndrome. Adv Exp Med Biol 2010;685:1-8.
6. Juhlen R, Landgraf D, Huebner A, Koehler K. Identification of a novel putative interaction partner of the nucleoporin ALADIN. Biology Open, 2016; 5:1697-05.
7. Brown B, Agdere L, Muntean C, David K. Alacrima as a Harbinger of Adrenal Insufficiency in a Child with Allgrove (AAA) Syndrome. Am J Case Rep, 2016; 17:703-6.
8. Vallet AE, Verschueren A, Petiot et al. Neurological features in adult Triple-A (Allgrove) syndrome. J Neurol 2012;259:39-46.
9. Vishnu VY, Modi M, Prabhakar S, et al. A motor neuron disease. J Neurol Sci 2014;336:51-3.
10. Dumic M, Barišić N, Kusec V, et al. Long-term clinical follow-up and molecular genetic findings in eight patients with triple A syndrome. Eur J Pediatr 2012;171:1453-59.
11. Sanjay D, Bhattarcharjee SA. A case of late-onset Allgrove syndrome presenting with predominant autonomic dys-

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function. Ann Indian Acad Neurol 2013;16:266-8.
12. Wenjing L, Chuxiu G, Zhan Q, et al. Identification of AAAS gene mutation in Allgrove syndrome: A report of three cases. Exper Therapeutic Med 2015;10:1277-82.
13. Tullio-Pelet A, Salomon R, Hadj-Rabia S, et al. Mutant WD-repeat protein in triple-A syndrome. Nat Genet 2000;26:332-5.
14. Huebner A, Yoon SJK, Ozkinay F, et al. Triple A syndrome - clinical aspects and molecular genetics. Endoc Res 2000;26:751-9.
15. Houlden H, Smith S, De Carvalho M, et al. Clinical and genetic characterization of families with triple A (Allgrove) syndrome. Brain 2002;125:2681-9.
16. Jain G, Choudhary A, Goyal M, Lal V. Achalasia and amyotrophic lateral sclerosis as part of Allgrove syndrome. Neurol India 2016;64:841-2.
17. Reimann J, Kohlschmidt N, Tolksdorf K, et al. Muscle pathology as a diagnostic clue to allgrove syndrome. J Neuropathol Exp Neurol 2017;76:337-41.
18. Prpic I, Huebner A, Persic M, et al. Triple A syndrome: genotype-phenotype assessment. Clin Genet 2003;63:415-7.
19. Bhashavan PV, Kumar KM, Rajendran VR, Fassaludeen AS. Allgrove syndrome—a syndrome of primary adrenocortical insufficiency with achalasia of the cardia and deficient tear production. J Assoc Physicians India 2003;51:726-8.
20. van Daele PL, de Herder WW, Huebner A. From gene to disease; adrenocortical insufficiency, achalasia and disrupted tear secretion: Allgrove syndrome. Ned Tijdschr Geneeskd 2002;146:2295-7.
21. von Rahden BH, Filser J, Seyfried F, et al. Diagnostics and therapy of achalasia. Chirurg 2014;85:1055-63.
22. Singer W, Low PA. Early orthostatic hypotension and orthostatic Intolerance-more than an observation or annoyance. JAMA Intern Med 2017. [Epub]
23. Lopes LS, Mürrer G, Lima NCP, et al. Orthostatic hypotension in elderly ambulatory patients. Arq Med ABC 2007;32:17-20.
24. de Carvalho M, Houlden H. Progressive bulbospinal amyotrophy in triple A syndrome with AAAS gene mutation. (Letter) Neurology 2002;59:1823.
25. Ledesma MC, Pérez M, López RR, Gómez EG. Síndrome de Allgrove (triple A). Hallazgo de una mutación no descrita en el gen AAAS. An Pediatr (Barc) 2013;78:109-12.
26. Misgar RA, Pala NA, Ramzan M, et al. Allgrove (Triple A) syndrome: a case report from the Kashmir Valley. Endocrinol Metab 2015;30:604-6.
27. Nakamura K, Yoshida K, Yoshinaga T, et al. Adult or late-onset triple A syndrome: case report and literature review. J Neurol Sci 2010;15:85-8.
28. Ikeda M, Hirano M, Shinoda K, et al. Triple A syndrome in Japan. Muscle Nerve 2013;48:381-6.
29. Brooks BP, Kleta R, Stuart C, et al. Genotypic heterogeneity and clinical phenotype in triple A syndrome: a review of the NIH experience 2000-2005. Clin Genet 2005;68:215-21.