Neuroendocrinology Letters Volume 37 No. 3 2016
ISSN: 0172-780X; ISSN-L: 0172-780X; Electronic/Online ISSN: 2354-4716
Web of Knowledge / Web of Science: Neuroendocrinol Lett
Pub Med / Medline: Neuro Endocrinol Lett

CASE REPORT

Allgrove syndrome with prominent neurological symptoms

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Submitted: 2015-11-27 Accepted: 2016-02-27 Published online: 2016-07-28

Key words: **achalasia; alacrima; adrenal insufficiency; ALADIN gene**

Neuroendocrinol Lett 2016; **37**(3):184–188 **PMID:** 27618595 NEL370316C02

Abstract

We report a young woman with the clinical picture of Allgrove syndrome in whom neurological symptoms are prominent. It usually presents in the first decade of life with a deficiency of tears, recurrent vomiting and dysphagia due to achalasia, severe hypoglycemic seizures and shock due to adrenal insufficiency. Neurological symptoms such as hyperreflexia, dysarthria, hypernasal speech, ataxia, sensory impairment, muscle weakness, and mental retardation are extremely slow to develop and manifest at a later age. Diagnosis was based on clinical presentation and laboratory findings. She is the first patient from the Czech Republic with genetic confirmation of Allgrove syndrome. This patient is one of about 100 cases described in the literature and one of the few patients with all the main typical clinical features.

Abbreviations:

AS	- Allgrove syndrome
ACTH	- adrenocorticotropic hormone
ALADIN gene	- alacrima achalasia adrenal insufficiency gene
BP	- blood pressure
CMCT	- central motor conduction time
DRPLA	- dentatorubral-pallidoluysian atrophy
FRDA	- Friedreich's ataxia
LUS	- lower esophageal sphincter
RNA	- ribonucleic acid
SCA	- spinocerebellar ataxia
SSRI	- selective serotonin re-uptake inhibitors
UES	- upper esophageal sphincter

INTRODUCTION

Allgrove syndrome (AS) (or 3A syndrome) is a rare autosomal recessive disorder (OMIM #231550), characterized by the triad of achalasia, alacrimia and adrenocorticotrophic hormone (ACTH)-resistant adrenal insufficiency (Allgrove *et al.* 1978). It has been suggested that this syndrome should be named 4A syndrome, with the addition of neurological manifestations (autonomic dysfunction, motor neuropathy, sensory disorder, mental retardation and similar neurologic diseases as the fourth component) (Gazarian *et al.* 1995). When both autonomic neuropathy and amyotrophy are present, it is called 5A syndrome (Synyal & Bhattacharjee 2013). Patients generally have between two to four of these major clinical symptoms. We describe a case in which the neurological symptoms were particularly prominent.

A number of associated features have been described in patients with AS, including palmoplantar and punctate hyperkeratosis, skin and mucosal hyperpigmentation, short stature, fatigue and muscle weakness, osteoporosis, xerostomia, angular cheilitis, glossitis and fissured tongue, delayed puberty, and microcephaly (Geffner *et al.* 1983; Stuckey *et al.* 1987; Dumic *et al.* 1991; Moore *et al.* 1991; Grant *et al.* 1992, 1993; Gazarian *et al.* 1995; Heinrichs *et al.* 1995; Hübschmann 1995; Chu *et al.* 1996; Clark & Weber 1998; Huebner *et al.* 1999; Zeharia *et al.* 1999; Bentes *et al.* 2001, Bustanji *et al.* 2015, Thomas *et al.* 2015).

CASE REPORT

A 36-year-old woman was referred to our department for evaluation of her progressive gait problems and dysphagia. She is the child of non-consanguineous parents. Her mother was diagnosed with multiple sclerosis at the age of 45. This diagnosis was confirmed by both positive oligoclonal bands finding in the cerebrospinal fluid and multifocal T2-weighted lesions in the white matter of both hemispheres on MRI. Her father was healthy. The patient's mother´s sister presents with gait disturbance and vertigo, although no definitive diagnosis has been given in this case. She lives in another state and is inaccessible for evaluation. The patient has two children. The 9-year-old son has a claw hand. Efforts were made to evaluate this clinical symptom, but the mother refused resolutely to allow it. The 7-year-old daughter is healthy. The patient´s delivery and early development were unremarkable. She was obese during early childhood. Her problems with swallowing solid meals, frequent vomiting and gastro-esophageal reflux started at the age of 4 and lead to growth failure. She was diagnosed with achalasia and the lower esophageal sphincter (LUS) muscle was surgically transected at the age of 6. The operation was repeated 1 year thereafter. The lack of tear production has been apparent since she reached adulthood and she did not notice it prior to that. Other remarkable symptoms were low blood pressure (60–80/40–60 mmHg) and presyncopes. She has noticed acral weakness in her legs since late childhood, although she was able to walk long distances. However, in recent years she has experienced fatigue after a 12 kilometer walk. She experienced acral numbness and muscle cramps. She underwent orthopedic correction for shortened tendons in her feet, with subsequent deformation of the digits, at the age of 29 (Figure 1). At the same time she perceived some loss of precise muscle control in her left hand and her muscle cramps became stronger. Dysphagia and hypernasal speech progressed. In the evenings she experienced diplopia and pain behind her eyes. She became short of breath when carrying out everyday activities. Her gait worsened in the dark. At night, she woke up sweating, but without a fever.

Clinical examination revealed asthenic habitus – BMI 16.3, hyperpigmentation of the skin (figure 2) and a scar in the left hypochondrium after an operation on the esophagus. A neurological evaluation found dry eyes and hypesthesia in the area of I.–III. branch of the left trigeminal nerve. Corneal reflexes were found to be normal, masseter reflexes were brisk. The tongue was atrophic with fasciculations. There was palatal paresis with absent gag reflex, with resultant difficulties in swallowing both solids and liquids. A nasal voice and dysphonia were evident. Fasciculations in the left biceps brachii, atrophied thenar and lumbrical muscles, weakness (4/5 of muscle test) of the hand muscles and proximal hypestesia were evident, predominantly on the left side. Pedes cavi, acral atrophies (Figure 1), diffused weakness of the legs (4/5 of muscle test), most prominently during plantar flexion of the foot, brisk tendon reflexes L2/4 and pyramidal signs were present bilaterally. Reflexes L5/S2 were absent. Fasciculations could be seen in the right thigh. Hypesthesia and mild ataxia of the left distal lower extremity and loss of vibration perception in the extremities were found. In standing position III, the patient titubated. Areas of hyperkeratosis and fine fissuring were present on both feet.

Previously performed tests included brain and cervical spine MRI, genetic testing (FRDA, SCA 1, 2, 3, 6, 7, 8, 12, 17, DRPLA), blood tumor markers, cerebral spinal fluid analysis (biochemical tests, oligoclonal bands, herpetic, borrelia and antiganglioside antibodies) and neuropsychological evaluation. The results of all these tests were normal.

A 3T brain MRI showed normal intracranial findings and atrophic lacrimal gland (Figure 3).

Electromyography revealed definite impairment of sensitive fibers conduction, this being lower and borderline in the upper extremities. The sensitive amplitude of the nervus suralis was reduced to 4.2 μV dx and 2.4 μV sin. Failure of synaptic transmission was excluded. In a needle study, chronic motor axonal impairment with signs of collateral re-innervation were found, without acute denervation. Somatosensory evoked potentials

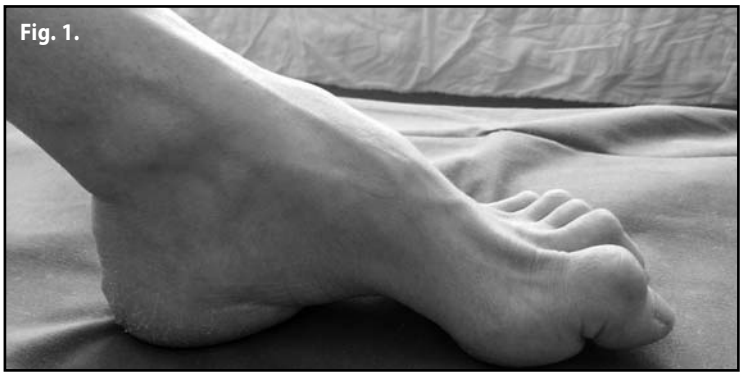
were diagnostic for the loss of sensitive fibers. The basic shapes of the evoked potentials were maintained, but were difficult to identify. The latency of the P40 wave was 43 ms. Motor evoked potentials were abnormal and proved serious dysfunction of the pyramidal tract in the central part of her proximal and distal extremities. Cortical latencies in the upper extremities were 34.5 ms on the right and 33.3 ms on the left (limit up to 24.8 ms). Central motor conduction time (CMCT) was 21.2 ms on the right and 19.1 ms on the left (limit up to 10.6 ms). Cortical latencies in the lower extremities were 46.4 ms on the right and 44.6 ms on the left (limit up to 34.6 ms). CMCT was 33.0 ms on the right and 30.4 ms on the left (limit up to 10.6 ms).

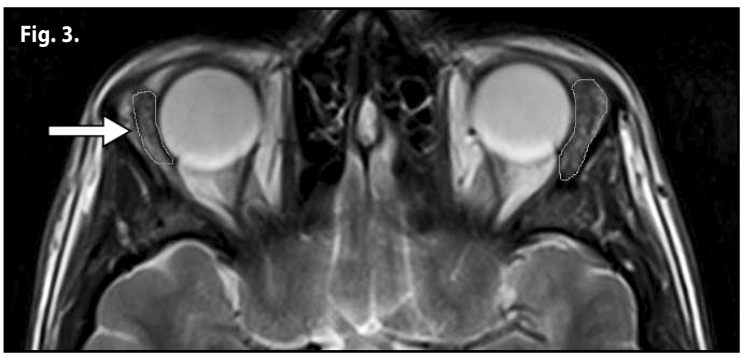
Ophthalmologic evaluation showed pallid conjunctiva, transparent hypoestetic cornea, slow pupillary reaction to light and convergence, without optic nerve atrophy. Fluorescein staining revealed considerable epitheliopathy of the whole extent of the conjuctivas and corneas. The lacrimal glands showed suspected redevelopment of cystic changes. The results of the Schirmer test (a semi-quantitative measure of tearing) were 1 mm/5 minutes bilaterally. Values showing less than 10 mm of wetting during this time are considered to be alacrima. The production of saliva was also decreased.

During the hospital stay, the patient`s blood pressure (BP) was 60–135/40–85 mmHg which was symptomatic of presyncopes. When erect, systolic BP decreased to about 50 mmHg and diastolic BP to 25 mmHg. Heart rate was 70–105 beats/min. The 30:15 ratio was 1.00 (below 1.00 is abnormal), the Valsalva ratio was 1.24 (below 1.10 is abnormal). Serum natrium, chloride, kalium and glucose levels were normal. Cortisol levels at 6 am were 307.60... 382.80 nmol/l (reference values 101.20–535.70), at 12 am 157.50...191.60 nmol/l (101.20–535.70), at 6 pm 91.60...118.50 nmol/l (79.00–477.80), at 12 pm 13.90...97.90 nmol/l (reference values 79.00–477.80). The value of cortisol at 13.90 nmol/l was very low. The level of adrenocorticotropic hormone was normal at 16.4 ng/l. Both renin and aldosterone levels were normal (50.31 pg/ml and 5.91 ng/l respectively).

Esophagoscopy results were compatible with non-advanced achalasia without spasm of the cardia. Manometry revealed normal integrated relaxation pressure (8.9 mmHg). Relaxation of the lower esophageal sphincter was partial, the gastroesophageal junction was patent. There was no motility (peristalsis or other contraction activity) during swallowing in the tubular esophagus. The tonus of the upper esophageal sphincter (UES) was close to the lower range of the normal limit (44.3 mmHg). The amplitude of contraction of the UES was reduced. Regurgitation was evident in 40% of contractions. These results were compatible with a diagnosis of aperistalsis according to the Chicago Classification. Computed tomography of abdomen showed normal findings, including normal size of the adrenals.

The patient signed an inform consent form for genetic testing, which was authorized by the Hospital Ethics Committee. The AAAS gene was analyzed by PCR and sequencing of both DNA strands of the entire





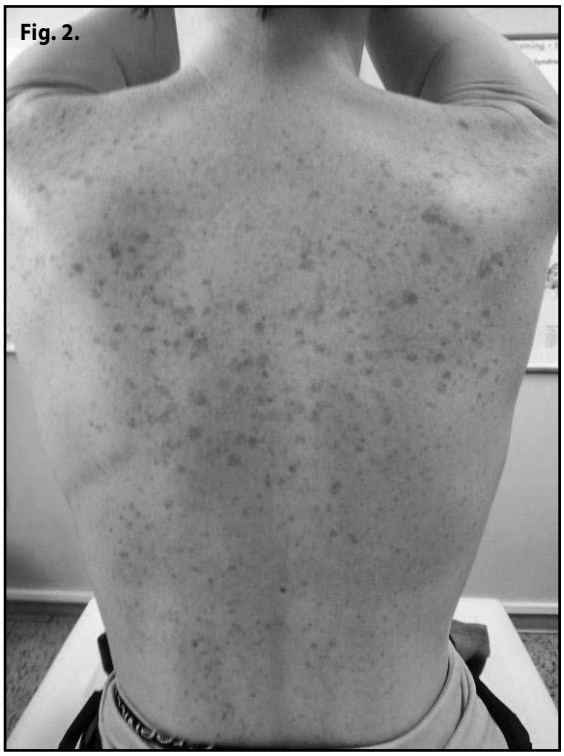


Fig. 1. Pes cavus with shortened tendons of the feet with subsequent deformation of digits.
Fig. 2. Hyperpigmentation of the skin.
Fig. 3. MRI showed atrophic lacrimal gland on the right.

coding region and the highly conserved exon-intron splice junctions. A heterozygous mutation in exon 1 of the AAAS gene (c.43C>A p.Gln15Lys) and a heterozygous mutation in exon 6 of the AAAS gene (c.464G>A p.Arg155His) were detected.

Treatment was symptomatic. The patient underwent surgical myotomia of the LES for achalasia and orthopedic correction of the shortened tendons of her feet for amyotrophy. She uses artificial tears and other lubricants for alacrima. We added 15 mg/day of hydrocortisone for adrenal insufficiency and prescribed SSRI after the diagnosis was completed. We needed to carry out a new fibroscopy for mild accent dysphagia after one year due to a discreet mycosis of the esophagus. Fluconazole was prescribed temporarily. If we notice worsened deformity of the feet, plastic surgery options will be investigated.

DISCUSSION

We have unique possibility to diagnose rarite Allgrove syndrome. AS is an autosomal recessive disorder and the AAAS gene is coded on the long arm of chromosome 12 (12q13) (Khelif *et al.* 2003). Mutation in the AAAS gene results in an insufficiency in the protein function known as aladin or adracalin. The AAAS gene belongs to the WD repeat protein family which exhibits a wide functional diversity that includes protein–protein interactions, signal transduction, RNA processing, vesicular trafficking, cytoskeleton assembly and cell division control (Neer *et al.* 1994; Smith *et al.* 1999). Part of the pathology is due to progressive loss of cholinergic function throughout the body (Bhargavan *et al.* 2003). Cells of AS patients show an altered induction or downregulation of genes associated with oxidative stress and antioxidant defense (Koehler *et al.* 2013). AS displays a familial cluster (Pedreira *et al.* 2004). It usually presents in the first decade of life with a deficiency of tears, recurrent vomiting and dysphagia due to achalasia, severe hypoglycemic seizures and shock due to adrenal insufficiency (Weber *et al.* 1996). Alacrima is considered to be an early symptom of AS, and appears during early infancy. (Bhargavan et al., 2003). In achalasia (the absence of peristalsis within the body of the esophagus) esophagography reveals a narrowing in the cardio-esophageal junction and a dilatation of the esophagus proximal to the junction (Weber *et al.* 1996). AS is one of the most common causes of adrenal insufficiency (Brett & Auchus 2015). Hormonal assessment reveals isolated glucocorticoid deficiency and ACTH insensitivity. Adrenal crisis can be precipitated by surgery, infection or trauma (Arun *et al.* 2014). Neurological symptoms such as hyperreflexia, dysarthria, hypernasal speech, ataxia, sensory impairment, muscle weakness, and mental retardation are extremely slow to develop and manifest at a later age. Hyperpigmentation of the skin and osteoporosis may appear, especially in adulthood (Soltani *et al.* 2007).

Diagnosis is based on clinical presentation and laboratory findings. Gene testing may be necessary to confirm the diagnosis in patients who exhibit just one or two of the main symptoms and/or screening of family members (Thomas *et al.* 2015).

CONCLUSION

This patient is one of about 100 cases described in the literature and one of the few patients with all the main typical clinical features. She is the first patient from the Czech Republic with genetic confirmation of Allgrove syndrome.

ACKNOWLEDGEMENT

The work was supported by Ministry of Health, Czech Republic – conceptual development of research organization (Nemocnice Na Homolce – NNH, 00023884), IG 154301. We are indebted to Carey Anne Vosecka for help with language editing.

Disclosure

The authors report no conflicts of interest in this work.

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