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ORIGINAL

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Case report of adult-onset Allgrove syndrome

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Abstract Allgrove syndrome is a rare autosomal recessive disorder characterised by childhood onset, alacrima, oesophageal achalasia, adrenocortical insufficiency, neurological and occasionally autonomic involvement. Although the disease has been associated with mutations in the ALADIN gene on chromosome 12q13, it is genetically heterogeneous. The case we report is interesting because of its onset in adulthood, long duration of disease and prominent neurological dysfunctions. After the onset of neurological abnormalities the diagnosis went unrecognised for years until the patient presented for evaluation of dysphagia. The presence of achalasia with dysphagia, adrenal insufficiency, reduced tear production, optic atrophy and peripheral motor-sensory neuropathy with axonal loss led us to clinically diagnose Allgrove syndrome even though a genetic study showed no mutations in the ALADIN gene exons. The case we report shares many clinical features with Allgrove syndrome and, even with the limitations of a single case, underlines the variability in this syndrome and the need for appropriate investigations along with a multidisciplinary approach.

Key words Allgrove syndrome • ALADIN • Oesophageal achalasia

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Introduction

Allgrove syndrome (OMIM 231550), also known as triple-A or 4A syndrome, is a rare autosomal recessive disorder with usual onset in childhood characterised by alacrima, achalasia, adrenal insufficiency, neurological disturbances and occasionally autonomic instability [1]. To date about 100 cases of Allgrove syndrome have been reported worldwide showing a considerable variability in disease severity and clinical manifestations. In most cases the disease first manifested in childhood with alacrima accompanied in 75% of the patients by achalasia [2]. Adrenal insufficiency usually begins after dysphagia and develops gradually over the first decade of life [3]. Neurological disturbances have a progressive course, and may affect the central, peripheral and autonomic nervous system showing heterogeneous and widely varying manifestations [1, 4, 5]. Homozygous or compound heterozygous mutations have been identified in the ALADIN gene which maps to chromosome 12q13 [6]. ALADIN encodes for a protein expressed in neuroendocrine, gastric and cerebral structures [1]. The disease

must, however, be genetically heterogeneous, as some case reports describe patients with Allgrove syndrome without ALADIN gene mutations [1, 7].

The case of adult-onset Allgrove syndrome [8] we describe is atypical for several features, such as the onset in adulthood, long duration of disease and the presence of prominent neurological dysfunctions, underlying the variability of this syndrome and hence the need for appropriate investigations along with a multidisciplinary approach.

Case history

A 37-year-old man presented with a 16-year history of neurological symptoms that had progressively worsened. He was the son of non-consanguineous healthy parents. His familial medical history was unremarkable for neuropsychiatric and other medical illnesses.

The patient was in good health until the age of 21 when he noticed weakness in dorsiflexion of his left foot followed rapidly by foot drop. In the ensuing years muscle weakness developed in both legs and arms. At the age of 28 years the patient began to complain of difficulty in swallowing solids and liquids. He also reported regurgitation of undigested food and saliva. The patient's clinical condition remained stable until the age of 30 when he complained of dizziness and a right foot drop developed. At the age of 35 years the dysphagia worsened and he began to experience paraesthesia and loss of skin sensitivity on his lower limbs and he complained of sexual impotence without reduced libido. When first seen by us he had been taking therapy with corticosteroids, prednisone 75 mg/day, since the age of 25 years because neurologists previously diagnosed dysimmune neuropathy. The patient reported that although corticosteroid treatment had improved the general hyposthenia, it had scarcely benefited the neurological deficits that slowly progressed over the years.

Neurological examination in our department showed marked distal muscle atrophy in the upper and lower limbs (Fig. 1); loss of strength in all four limbs, marked loss of vibration sense in the lower limbs, bilateral foot drop, and loss of position and movement sensation in both lower limbs. Tendon reflexes were absent. There were no cranial nerve abnormalities.

The laboratory investigations including serology for several viruses and immunological screening tests yielded negative or normal findings. The adrenal function study and hormone tests showed a reduced blood level of adrenocorticotropic hormone (ACTH) and testosterone and increased urinary cortisol (Table 1), probably due to long-term corticosteroid therapy. On the patient's admission to hospital we tried to reduce the corticosteroid dose, but follow-up blood and urinary tests showed that the adrenal function failed to be restored. Cerebrospinal fluid examination disclosed normal findings.

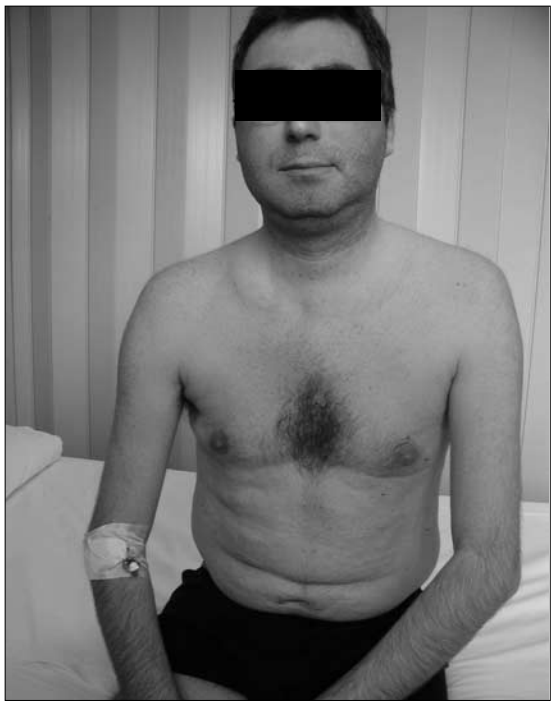

Fig. 1 Marked distal muscle atrophy

Electrocardiogram, chest X-ray, magnetic resonance imaging scans of the head and spinal cord were normal. Needle electromyography of limb muscles disclosed diffuse loss of motor units, with large and polyphasic motor units; fibrillation potentials and positive sharp waves were observed in all four limbs, in diaphragm and intercostal muscles. Sensory and motor nerve conduction study disclosed axonal neuropathy (Table 2). Somatosensory evoked potentials were bilaterally absent at the cortical and peripheral level. The blink reflex was normal. Genetic testing to evaluate the mutation for spinal and bulbar muscular atrophy or Kennedy's disease, an X-linked neurodegenerative disease caused by an expansion of a polymorphic tandem CAG repeat within the androgen receptor gene on chromosomal locus Xq11-q12, was negative.

Histological examination of a deltoid muscle biopsy specimen showed a pattern of neurogenic atrophy. Ophthalmologic investigation disclosed an atrophic optic nerve papilla more pronounced in the right eye, with reduced optic acuity (6/10 bilaterally). The Schirmer test showed reduced tear production, 0 mm in the right at 3 and 5 min and 3 mm in the left eye at 3 and 5 min. Despite the severely reduced tear production, the patient did not complain of ocular symptoms.

A barium radiographic study showed a dilated oesophagus (Fig. 2): normal peristalsis had been replaced by vigorous tertiary contractions. The upright film showed an air-fluid level. The distal portion of the oesophagus showed

Table 1 Values of the hormonal level of the blood and urinary samples

Hormone	Results	Normal values
Oestradiol	13.90 pg/ml	(25–107)
FSH	6.01 mU/ml	(1.37–13.58)
LH	3.55 mU/ml	(1.26–10.5)
Prolactin		
Basal	8.06 ng/ml	(2.58–18.12)
15’	13.30	
30’	11.00	
Sex hormone-binding globulin (SHBG)	16 nmol/l	(9–54)
Testosterone	0.93 ng/ml	(1.56–8.77)
Testosterone free	4.71 pg/ml	(8.9–42.5)
ACTH*		
Hour 8	3.96 pg/ml	(10–90)
Hour 10	4.28	
Hour 12	6.20	
Cortisol*		
Hour 8	35.0 ng/ml	(50–250)
Hour 10	23.9	
Hour 12	21.3	
Urinary cortisol	1732 µg/24 h	(10–100)

*Circadian rhythm during 24 hours

only occasional cardia opening with a persistent beak-like-narrowing, and a marked delay in oesophageal clearing. Films obtained in the prone and standing positions showed evidence of oesophago-pharyngeal reflux. These findings led to a diagnosis of oesophageal achalasia, confirmed by oesophageal manometry. Lung-function tests revealed a restrictive respiratory defect. Postural stress tests to evaluate autonomic dysfunction evidenced no abnormalities.

For genomic analysis, DNA was extracted from peripheral blood leucocytes using the NucleoSpin Blood L Kit (Mackerey-Nagel). The 16 exons and the intron exon junctions of the ALADIN gene were amplified in 12 polymerase chain reaction (PCR) 242-550 base pair (bp) fragments. Target sequences were amplified by PCR from 300 ng of genomic DNA, using oligonucleotide primers. The PCR product was checked by electrophoresis on a 1% agarose gel containing ethidium bromide to make sure that PCR amplified only the specific product and no additional band. Direct DNA sequencing of the amplified products was carried out with a Big Dye Terminator Cycle Sequencing kit and an ABI-PRISM 3100 Genetic Analyzer (PE Applied Biosystem, Foster City, CA, USA). Forward and reverse sequences were analysed and compared with the genomic reference sequence (NM_015665). Besides some polymorphic variations, sequencing identified no mutations in the ALADIN gene exons. The patient’s parents were not available for genetic examination but were understood to have been normal.

Table 2 Motor and sensory nerve conduction velocities

Motor					Sensory	
Nerve	Latency (ms)	Amplitude (mV)	Morphology	VCM (m/s)	Amplitude (µV)	VCS (m/s)
Median R	3.4	3.1	Biphasic	48	2	48
Median L	4.0	2.8	Biphasic	47	Absent	
Ulnar R	2.8	0.5	Biphasic	47	2.2	49
Ulnar L	2.7	0.4	Biphasic	47	1.6	43
Peroneal R	5.3	0.1	Biphasic	39		
Peroneal L	Absent					
Medial plantar R	5.1	0.1	Biphasic	–		
Medial plantar L	Absent					
Sural R					Absent	
Sural L					3	38

VCM, motor nerve conduction; *VCS*, sensory nerve conduction

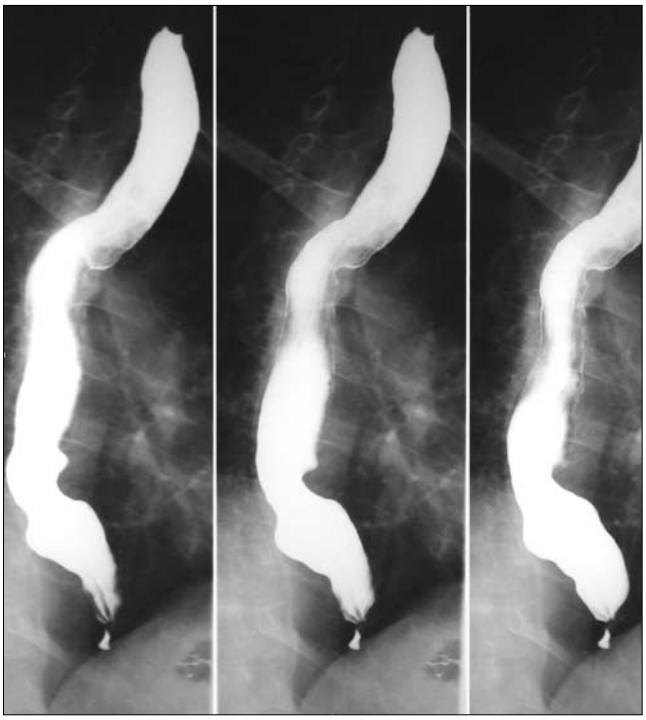

Fig. 2 Barium radiographic study showing an air-fluid level, and a dilatation in the distal oesophagus

Discussion

To our knowledge this is the first description of an Italian patient with Allgrove syndrome manifesting neurological symptoms only in adulthood and diagnosed years later during investigation of dysphagia.

When we first saw the patient at the age of 37 years he was unable to walk without support and his difficulty in swallowing had worsened over the previous months. The neurophysiological findings at first suggested hereditary sensory-motor neuropathy type II C (HSMN II C). Arguing against this diagnosis was our patient's dysphagia, a symptom never present in HSMN II C [9]. Because of the adult onset and slow progression of the neurological symptoms with weakness, loss of vibration sense in the lower limbs, absence of tendon reflexes and small or absent sensory nerve action potentials, we also considered Kennedy's disease. The patient presented with dysphagia but not other bulbar dysfunction and the distal distribution of muscle atrophy without face or tongue atrophy, and the absence of tremor and gynaecomastia arguing against this hypothesis. Moreover, the genetic test disclosed no expansion within the androgen receptor gene. Finally, we considered other possible differential diagnosis including amyloidosis and neuropathy with autonomic involvement. However, muscle biopsy was negative for deposits of amyloid [10], and the patient presented no signs of systemic manifestation or autonomic system involvement.

The case we report shares many clinical features with Allgrove syndrome. Although the genetic study showed no mutations in the ALADIN gene exons, the reason that led us to clinically diagnose Allgrove syndrome was the presence of achalasia with dysphagia, reduced tear production, optic atrophy, peripheral motor-sensory neuropathy with axonal loss and adrenal insufficiency. The clue to the diagnosis of Allgrove syndrome came from the radiological study of the oesophagus documenting achalasia and from ophthalmologic investigation disclosing severe alacrima. Oesophageal achalasia is found in about 75% of patients with Allgrove syndrome and is usually the first symptom for which patients seek medical help [3,5]. Ophthalmologic investigation disclosed an atrophic optic nerve papilla more pronounced in the right eye with reduced optic acuity and severely reduced tear production. Other usual features of Allgrove syndrome are adrenal insufficiency, the main cause of death in this syndrome [5], and dysautonomic signs. The patient we describe had been taking prednisone 75 mg/day since he was 25 years old and his blood and urinary samples showed adrenocortical insufficiency. The fact that corticosteroid treatment improved his general status could suggest that adrenal insufficiency preceded corticosteroid treatment. However we could not decrease the dosage of prednisone, and we interpreted this difficulty as an adrenal gland insufficiency after years of corticosteroid treatment. Another distinctive feature in our patient is that achalasia was the only sign of autonomic nervous system dysfunction. Postural stress tests to evaluate autonomic cardiovascular dysfunction disclosed no abnormalities, and the bladder was unaffected. Finally, his sexual impotence probably depended on the low serum level of testosterone secondary to the adrenocortical insufficiency but could also be another sign of dysautonomia.

The reason our case is of interest is that it lacks the common chronological course and the typical presenting symptoms of Allgrove syndrome. The disease had its onset in adulthood with prominent, disabling neurological impairment throughout the disease course and apparently sparing the autonomic nervous system usually involved at the onset. An unusual feature was that the oesophageal achalasia went undiagnosed for more than 10 years after the onset of swallowing dysfunction. Finally, despite the severely reduced tear production, the patient reported no ocular disturbance and it was disclosed only by paraclinical tests [11], probably because the patient was more concerned with problems such as motor impairment.

The fact that genetic testing identified no ALADIN gene mutation in this patient does not exclude a clinical diagnosis of Allgrove syndrome, because the disease presents genetic heterogeneity. The absence of gene mutations has already been reported in two families with the full triple A syndrome phenotype [1]. Another possibility is that we failed to identify ALADIN mutations because they lie in gene regions we did not sequence, such as the pro-

moter and untranslated regions. Exon sequence analysis cannot of course identify possible non-overlapping complete exon deletions. Aladin gene deletions, however, are not reported in the Human Gene Mutation Database for the ALADIN gene.

In conclusion, the case we report shares many clinical features with Allgrove syndrome and even with the limitations of a single case, underlines the variability of this syndrome and the need for appropriate diagnostic investigations along with a multidisciplinary approach.

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