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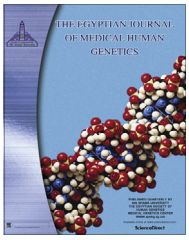

CASE REPORT

Allgrove syndrome: an Egyptian family with two affected siblings

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KEYWORDS

Achalasia;
Alacrima;
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Abstract *Background:* Allgrove or AAA (Triple A) syndrome is a rare autosomal recessive disease characterized by achalasia, alacrima, adrenocorticotrophic insufficiency and some neurologic abnormalities.

Case report: Here we report two brothers 13 and 15 years old, with variable features of the syndrome, with prominent neurological symptoms which started in the first decade and, led to motor paralysis and severe muscle wasting in the elderly brother in the second decade of life. Moderate achalasia developed at 9 years in the older brother and showed a slowly progressive course with development of chest pain and dysphagia. Alacrima was not evident before the age of 12 years.

The neurological symptoms were less severe in the younger brother. He suffered alacrima that started at age of 11 years and mild dysphagia due to achalasia at age of 12 years, both being slowly progressive.

This paper highlights early features of this syndrome among Egyptian population and the importance to exclude Allgrove syndrome in the presence of progressive neurological dysfunction.

To conclude: Allgrove syndrome should be suspected in patients with neurological impairment associated with any of the main symptoms of the syndrome (alacrima, achalasia and adrenal insufficiency).

1. Introduction

Allgrove's syndrome is a rare autosomal recessive disorder, which is characterized by many features with alacrima, achalasia, autonomic disturbance, and ACTH insensitivity being the common features [1]. Other features that may present during the first decade of life include severe (occasionally fatal) hypoglycaemic or hypotensive attacks, related to adrenocortical insufficiency. Cholinergic dysfunction and autonomic tests are usually disturbed with a significant deviation from normal values [2].

Sometimes adrenal insufficiency or other features may be delayed to adulthood, but adult cases with Allgrove's syndrome commonly present with neurological disease that affects multiple neurological systems [3].

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The neurological symptoms are variable and may affect the central, peripheral and autonomic nervous system [4,5]. Serious reported neurological manifestations include dementia, Wernicke's encephalopathy [6], optic atrophy, cerebellar ataxia, and Parkinsonism [7].

The syndrome has been mapped to a 6 cm interval on chromosome 12q13 [8]. The disease is thought to be caused by mutation in the AAAS gene on chromosome 12q13, which encodes ALADIN protein (a part of the nuclear pore complex), resulting in an impaired protein function. Other changes in the AAAS gene include a missense mutation p.R155H, c.618delC, and p.Ser207fs [9].

The exact biological effect of the impaired ALADIN protein is unknown, some evidence showed that the fibroblasts of 4A syndrome patients have a higher basal reactive oxygen species (ROS) level and an increased level with an increased sensitivity to oxidative stress [10]. Further studies are still needed to elucidate the precise cellular/molecular pathways that are disturbed in this disorder.

The aim of this case report is to describe two Egyptian brothers with Allgrove syndrome, with different clinical presentation and different age of the onset.

Consent of the parents as well as the ethics committee of the National Research Centre (NRC) was obtained.

2. Case report

Here we describe a family who has two diseased male siblings, and parents are first cousins (Fig. 1). They are 13 and 15 years old and the symptoms started around the age of 6–7 years (Table 1). In the older brother, impaired sensation and progressive muscle weakness (more prominent in lower limbs) started at 7 years. Then ataxic gait developed at around 12 years with progressive muscle wasting, lost deep reflexes, mildly impaired superficial reflexes and development of ataxic gait. Eye examination showed mild corneal dryness, normal fundus and visual evoked potential.

In the younger brother neurological symptoms started at the age of 9 years with impaired muscle power and superficial sensations in the lower limbs with mild affection in the upper limbs. The course was slowly progressive until the age of 13 years with decreased muscle tone and development of ataxic gait (other cerebellar signs are not prominent). Eye examination showed normal fundus and visual evoked potential (VEP). Cranial nerves were intact in both cases.

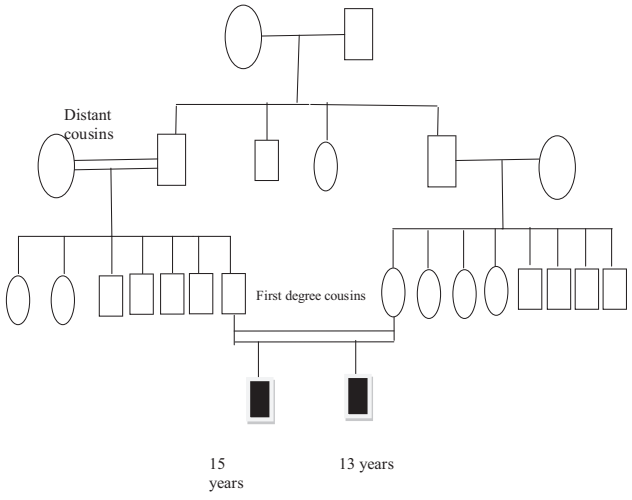

Figure 1 Pedigree of the family with two siblings having Allgrove syndrome.

Mixed axonal and dendritic peripheral neuropathy signs are evident by nerve conduction tests (NCT). Achalasia is present in both cases and started in the first decade of life being moderately progressive and then chest pain developed in the older brother. Alacrima is present in the older case and is mildly detected in his brother. Genital examination revealed small testicles and penis with sparse pubic and axillary hair (stage 2 puberty), reflecting adrenocortical insufficiency. Resting blood pressure was within normal ranges with slightly impaired pressor test and standing blood pressure.

Some dysmorphic features were seen; low set ears, short neck, down slanting palpebral fissures of the eyes, low posterior hairline. Dermatological signs in the form of hyperkeratosis of palms, low inserted thumb are present in the younger brother (in both hands). In the older brother, short neck and low posterior hairline were seen.

3. Discussion

The prevalence of Allgrove syndrome is unknown, only scattered family and case reports were noted in the literature. An autosomal recessive inheritance of Allgrove syndrome is suspected with variable presentation. No evidence suggests that gender affects the frequency.

The three main features of the disease are adrenal insufficiency (presented by hypoglycaemia or hypotension), alacrima that leads if severe to keratopathy and corneal melting and achalasia leading to frequent vomiting or regurgitation. Alacrima was considered the most early and consistent feature [11]. It is worth mentioning that previous follow up studies for children with dysphagia and symptoms of achalasia revealed most cases as isolated cases without other symptoms of Allgrove syndrome, while alacrima being a more constant feature [12].

In Allgrove syndrome, usually normal ACTH level is found in blood while cortisol level is subnormal and/or showing disturbances in diurnal variation, which is explained by ACTH resistance [13]. Our cases show normal ACTH and decreased morning and evening cortisol level in blood.

A factor that also plays a role in the difficult determination of the prevalence of the syndrome is its variable presentation, including unexplained childhood death due to adrenal crisis or mild disease that is not apparent until adulthood. Developmental delay could be the sole prominent presentation of the syndrome.

The cases presented in this study showed the features of Allgrove syndrome during first decade in life with the neurological symptoms being the earliest manifestation, with decreased muscle power, sensation and deep reflexes in both brothers (more progressive in the elderly sib). In addition, cerebellar signs were clear.

Minimal signs of autonomic neuropathy are present in both sibs. Although, alacrima and achalasia developed over a slowly progressive course, they were overlooked by the significant neurological impairment.

The neurological disturbances associated with Allgrove syndrome are variable and a previous study showed that all

Table 1 Clinical findings and investigations in the 2 Allgrove cases.

	Case 1	Case 2
History		
Age	15 years	13 years
Achalasia	+ve (moderate)	+ve (mild)
Alacrima (confirmed by Schirmer test [15])	+ve (moderate)	+ve (mild)
Neurological symptoms		
Motor power	Grade II	Grade III
Sensation	↓↓ in lower limbs	↓ in lower limbs (LL)
Muscle tone	↓ Moderately	↓ mildly
Muscle wasting	Severe	Moderate
Superficial reflexes	↓ Mildly	Intact
Deep reflexes	Lost ankle, ↓ knee	Lost ankle
Cranial nerves	Normal	Normal
Cerebellar signs	+ve (ataxic gait, finger to nose and heel to chin test)	+ve (ataxic gait, mildly other tests)
Fundus	Normal	Normal
Cardiovascular autonomic: lying BP–standing BP	130/85–125/85	120/75–125/65
Pressor tests		
Cutaneous cold: lying BP–standing BP	125/85–120/85	125/70–115/75
HR	75–85	73–80
Exercise stimulation (lying BP–standing BP)	130/85–125/85	135/75–105/70
Investigations		
Serum cortisol		
Morning(AM)	2.2 μg/dL ($n > 4.0$)	<1.0 μg/dL ($n > 4.0$)
Evening (PM)	1.6 μg/dL ($n > 3.0$)	1.2 μg/dL ($n > 3.0$)
Serum ACTH		
AM	25 pg/ml ($n < 50$)	22.9 pg/ml ($n < 50$)
PM	27.7 pg/ml ($n < 40$)	26.8 pg/ml ($n < 40$)
Electromyography(EMG): biceps–triceps–tibialis ant-quadriceps	Duration polyphasic action potential (AP), ↓ interface	Fibrillations, ↑ duration polyphasic AP
Nerve conduction study (NCS)	↓ Amplitude ↓ Nerve conduction velocity (NCV) in UL nerves Absent in LL nerves (e.g. tibial n.)	↓ Amplitude and NCV in UL and LL.
Karyotype	Normal	Normal

BP stands for blood pressure, HR stands for heart rate, NCV stands for nerve conduction velocity, NCV stands for nerve conduction velocity, AP stands for action potential.

included patients showed motor neuron signs (100%), while sensory disturbance and autonomic dysfunction were represented in 29% and 57% of patients successively [7]. A previous Egyptian study reported myopathy in a 13 year old boy with Allgrove syndrome [14].

Although our cases do not show prominent clinical autonomic dysfunction, they were diagnosed as Allgrove syndrome due to a combination of neurological dysfunction, alacrima and achalasia. Laboratory tests confirmed decreased cortisol level (adrenocortical insufficiency).

Increased awareness of the disease specific symptoms and signs is required for proper diagnosis, to avoid the serious manifestations reported which include hypoglycaemia due to adrenocortical insufficiency, and shock due to autonomic neuropathy and adrenocortical insufficiency.

Our data suggest a careful assessment of children with multisystem neurological disturbances. Allgrove syndrome should be suspected in patients with multiple aspects of neurological impairment.

It should be especially considered in patients who show a combined phenotype of motor neuron disease, sensory/autonomic disturbance, and cerebellar signs, as the symptoms of the syndrome would start with mild severity in the first decade of life and then progress rapidly leading to severe neurological impairment and handicap.

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