Case Report

Iran J Pediatr
Mar 2010; Vol 20 (No 1), Pp:101-106

Premature Loss of Permanent Teeth in Allgrove (4A) Syndrome in Two Related Families

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Received: *Feb 07, 2009*; Final Revision: *Apr 27, 2009*; Accepted: *May 06, 2009*

Abstract

Background: Allgrove syndrome is a rare autosomal recessive condition characterized by adrenal insufficiency, achalasia, alacrima and occasionally autonomic disturbances. Mutations in the AAAS gene, on chromosome 12q13 have been implicated as a cause of this disorder.

Case(s) Presentation: We present various manifestations of this syndrome in two related families each with two affected siblings in which several members had symptoms including reduced tear production, mild developmental delay, achalasia, neurological disturbances and also premature loss of permanent teeth in two of them,

Conclusion: The importance of this report is dental involvement (loss of permanent teeth) in Allgrove syndrome that has not been reported in literature.

Iranian Journal of Pediatrics, Volume 20 (Number 1), March 2010, Pages: 101-106

Key Words: Achalasia, Adrenocortical Insufficiency, Alacrimia (Allgrove, triple-A) Protein, Human; AAAS Protein, Human; Teeth; Allgrove Syndrome; Triple A Syndrome Protein, Human

Introduction

In 1978 Allgrove and colleagues described 2 unrelated pairs of siblings with achalasia and ACTH insensivity, three had impaired lacrimation and one also had autonomic dysfunction. This triad (achalasia, adrenal insufficiency and alacrima) became known as Ttriple A Syndrome [1].

During the following years several reports in the literature have focused on more global autonomic disturbances associated with Allgrove syndrome leading one author to recommend the name 4A syndrome (adreno-cortical insufficiency, achalasia of cardia, alacrima and autonomic abnormalities)[2-4]. There is significant variability in the clinical presentation [5].

Additional features included hyper-reflexia, muscle weakness and nasal speech. Incidence is unknown and only few numbers of families and case reports exist in literature. Inheritance is

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autosomal recessive and most patients have consanguineous parents [6], but autosomal dominant forms with incomplete penetrance have also been reported [7,8]. Parental consanguinity and previously affected siblings are the primary risk factors.

Mutations in the AAAS gene, which encodes the product aladin, on chromosome 12q13 have been implicated as a cause of this disorder. This gene belongs to WD-repeat regulatory protein family which exhibits wide functional diversity. The encoded protein, aladin, may help regulate nucleo-cytoplasmic transport of other proteins. High expression of this protein is seen in the adrenal gland, brain and gastrointestinal tract, the organs in which the main pathologic manifestations of disease occur[9-14]. Some authors believed that the pathology of this condition may be due to a progressive loss of cholinergic function throughout the body [8,15].

Age at onset of symptoms is variable but patients usually present during the first decade of life with hypoglycemia, adrenal crisis or dysphagia. Achalasia or alacrima may precede adrenal insufficiency. Adult patients with 4A syndrome may present with multisystem neurological disease [4].

This article reports two pairs of siblings in two related families with broad clinical features of the syndrome with particular attention to premature loss of permanent teeth in two siblings.

Case(s) Presentation

Family 1

Case 1: A 13 year-old girl with unremarkable birth history was referred to our endocrinology clinic for further follow up. She was diagnosed with familial gluococorticoid insufficiency at age 4 after a hypoglycemic seizure with low cortisol and elevated ACTH level and was discharged on oral prednisolone. Her parents were cousins and she was born at term.

Review of systems was positive for crying without tears from early infancy and darkening of skin at age 4. By age 7 she was felt to have poor school performance and learning difficulties. There was loosening of permanent teeth when she was l0 years old, and became near totally edentulous by the age of 13 years. She was also suffering from muscular wasting and weakness. Her sister had achalasia and hearing deficits.

On physical examination she was found to be of short stature and delayed in response. Blood pressure was normal without orthostatic hypotension, weight 25 kg (Z score -3 SD), height 132 cm (Z score -4 SD) according to NCHS growth chart. Pubertal stage: breast SMR (sex maturity rating) 1 and pubic hair SMR 2 according to Tanner's staging system.

She had a distinct facial appearance consisting of narrow upper lip and down–turned mouth with nasal speech. The patient was near totally edentulous. There was distal wasting in the arms, lower limb, and significant weakness of the legs.

Her past hospital records - before treatment with prednisolone– showed normal thyroid function tests and routine biochemical and hematological tests. Serum glucose was low (30 mg/dL). Serum cortisol was 1.5 µg/dL (normal range 5-20) before, 3 µg/dL 30 minutes and 2 µg/dL 4 hours after intramuscular injection of 250 µg long acting ACTH. (Normal response: peak plasma cortisol level greater than 19 µg/dL).

Ophthalmologic evaluation and Schirmer test revealed alacrima. Barium esophago-gram did not demonstrate achalasia.

The clinical finding was typical for Allgrove syndrome.

Case 2: This 15-year-old girl was second sibling of case 1 who was born of consanguineous parents. She first presented with vomiting and difficulty in swallowing at age 5 and subsequently underwent esophageal dilatations for achalasia.

She lost her teeth prematurely one by one at age 13. She also was noted to have learning difficulties, poor school performance and hearing deficit.

On examination she was mentally disabled and had dysmorphic facial features with nasal speech. She was partially edentulous. Blood

pressure, weight and height were normal. Breast and pubic hair were in SMR 2. Additional findings were muscular wasting, weakness and alacrima.

Bilateral hearing loss was confirmed by hearing evaluation. Routine biochemical, hematological and serum cortisol level before and after ACTH stimulation test were normal.

Neither of the two patients had significant dental caries or periodontal disease, we did not find abnormal results in clinical and laboratory investigations for their teeth loss.

Achalasia and alacrima were valuable clues to speculate that she had Allgrove syndrome.

Family 2

Case 3: A 6-year old boy born to consanguineous parents (cousin to cases 1 and 2) was referred to our clinic with darkening of skin, developmental delay and photophobia. Hyperpigmentation over the knuckles of the hands and feet had developed gradually over the last 12 months. The patient's past medical history was significant for esophageal surgery and cardiomyotomy for achalasia manifested by recurrent vomiting.

On physical examination long thin face with long philtrum, narrow upper lip characteristic of Allgrove syndrome was observed. He was mentally disabled. The weight was 16.5 kg (Z score -2.5 standard deviation) and the height was 103 cm (Z score -3 standard deviation). Neurologic findings consisted of dysarthria, and mild gait disturbance. Heart rate was 90/min and blood pressure 100/60 mmHg in supine position, but he had marked postural fall in both. (60/min and 70/40 in upright position, respectively). Schirmer's test revealed right eye 4 mm and left eye 2 mm of wetting (alacrima was confirmed).

Serum Na, K, aldosterone, renin, thyroid function tests, BUN, and creatinine were normal. Serum ACTH level was high normal (53 pg/ml; reference range 9-52 pg/ml). serum Cortisol was 2.6 µg/dL before, 4 µg/dL 30 minutes and 2 µg/d 4 hours after ACTH stimulation respectively. Plasma levels of cortisol was measured by chemiluminescence, serum aldosterone and ACTH by radioimmunoassay, and rennin by immunochemiluminescence assay.

Based on these findings, Allgrove syndrome diagnosis was established.

Case 4: This 10-year-old patient is older sister of case 3 and was born with unremarkable birth history. She was evaluated because of reduced tear production and positive history of Allgrove syndrome in her brother. At age 2 she was noted to have prominent neuro-developmental delay (delay in sitting, walking and speech). She had not attended school normally because of learning difficulties.

On examination she was normal for weight, height and blood pressure without orthostatic changes. Clinical findings included distinct facial appearance characteristic of Allgrove syndrome, nasal voice, dysarthria, mental retardation, ataxia (tandem gait and finger-to-nose testing was disturbed). Slit lamp examination and ophtalmoscopy were normal, but Schirmer's test typically showed alacrima. Barium esophagogram did not show dilated esophagus. Biochemical, hormonal and hematological screening were negative except for low cortisol and blood sugar and high ACTH (serum glucose 40 mg/dL, serum cortisol 3.4 µg/dL, 4 µg/dL, and 2.4 µg/dL, immediately before, 30 minutes and 4 hours after intramuscular injection of 250 µg long acting ACTH, respectively). ACTH level was 60 pg/ml. In the light of these findings a diagnosis of Allgrove syndrome was considered. Clinical findings in patients are summarized in table 1.

Discussion

When adrenal insufficiency is seen in conjunction with reduced lacrimation, achalasia of cardia and autonomic neuropathy, the condition is referred to as 4A syndrome. It is a form of primary adrenal insufficiency, commonly without mineralo-corticoid deficiency. Affected patients have between two and four of these main criteria, but a wide spectrum of associated features have been described including progressive central, peripheral and autonomic nervous system

Table 1: Clinical findings in 4 patients with Allgrove syndrome

Case	1	2	3	4
Age	13	15	6	10
Sex	Female	Female	Male	Female
Dysmorphic facial features	+	+	+	+
Achalasia	-	+	+	-
Alacrima	+	+	+	+
Cortisol deficiency	+	-	+	+
Salt loss	_	_	_	_
Hyperpigmentation	+	-	+	_
Impaired intelligence	+	+	+	+
Hearing deficit	_	+	_	_
Short stature	+	_	+	_
Delayed puberty	+	+	_	_
Ataxia	_	_	+	+
Muscle weakness, wasting	+	+	-	-
Dysarthria	_	_	+	+
Nasal speech	+	+	+	+
Autonomic dysfunction	_	_	+	_
Teeth loss	+	+	_	_

abnormalities, amyotrophic lateral sclerosis, pyramidal syndrome, distal motor neuropathy, dystonia, chorea, micro-cephaly[6,16-19,20], angular cheilitis, pes cavus[19], short stature[20], hearing deficit[8], xerostomia[21], and palmo-plantar hyper-keratosis[22].

Most cases present with classic symptoms of adrenocortical insufficiency including hypoglycemic seizures or hypotensive attacks, less frequently, a child may be evaluated initially for recurrent vomiting, hyperpigmentation, or developmental delay[2].

We believe that clinical evaluation met the criteria for the diagnosis of Allgrove syndrome in our patients. Impaired intelligence, similar facial appearance characteristic of Allgrove syndrome and alacrima were the most consistent clinical signs of the syndrome in our patients.

Lack of lacrimation was frequently present from early infancy and almost invariably before age 5 years. One patient had photophobia. In review of literature alacrima was the earliest and most consistent clinical sign of Allgrove syndrome[6,22].

We identified a spectrum of associated neurologic features in our cases including: impaired intelligence in all cases, significant autonomic dysfunction in case 3, muscular wasting and weakness in case 1 and, 2, ataxia in case3, 4, dysarthria in case 3 and 4. Kimber described two families who exhibited signs of multisystem neurological disease including hyperreflexia, muscle wasting, dysarthria, ataxia, optic atrophy, and intellectual impairment[4]. Kurca reported epilepsy, autonomic neuropathy and damages of central and peripheral nervous system in two brothers[23]. Chávez et al described a 21-year-old man with hyper-reflexia and muscle weakness with Allgrove syndrome[19]. Deumic focused on progressive autonomic and motor neuropathy in this condiction[24].

Our cases are remarkable in that all patients show evidence of intellectual impairment which was suggested by clinical history and confirmed by neuropsychometry. Cognitive problems have been reported in some pediatric patients with Allgrove syndrome in literature (Kimber et al 2003, Grant et al 1993, Moore 1991, Khalifa 1988)[2,4,6,25], but

it is unclear if this is a primary feature of the Allgrove syndrome or simply a reflection of recurrent hypo-glycemia.

With one exception all patients had adrenal insufficiency. Glucocorticoid deficiency is hallmark of this syndrome and develops during the first two decades of life, progression from normal adrenal function to adrenal insufficiency has been described in a number of individuals[6,11,15].

It remains to be seen if case 2 will go on to develop adrenal insufficiency. Lack of adrenal insufficiency or achalasia does not negate this diagnosis[6,8,15]. .

Two of our cases differed from other cases with premature loss of permanent teeth. We did not find possible causes of premature loss (trauma, osteomyelitis, peri-odontal infection, xerostomia, dental caries were ruled out). We speculate this to be also a feature of Allgrove syndrome.

The literature was reviewed for loss of teeth associated with this condition but it has not been described by previous investigators. Teeth loss points to the multisystemic character of the disorder.

Chu has reported periodontal disease, multiple caries, and dry mouth in a 16-year-old Hispanic boy[8]. Vucicevic-Boras reported Allgrove syndrome in a 14-year-old female with xerostomia[21].

Finally, case 2 had hearing deficit which has been previously reported[8].

Case 3 and 4 are currently on treatment with hydrocortisone and topical ocular lubrication with periodically follow up visits. Case 1 who was the first diagnosed patient died at age 14 after a heavy stress condition (status epilepticus) although she received stress doses of hydrocortisone). By case 2 the parents disclaimed periodical follow up.

Conclusion

We suspect that in addition to known previous manifestations, 4-A syndrome can particularly present with loss of permanent teeth without dental caries. This could be the first report of an unusual presentation of Allgrove syndrome in literature.

Acknowledgment

The authors would like to thank parents of patients for their willing cooperation and Mrs Setare, head nurse of pediatric ward in Be'ssat Hospital for blood sampling.

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