

Allgrove's Syndrome: Two Case Reports and Review of Literature

Daniel Zamanfar,^{1,*} Elika Shokri,² Shiva Shadani,² and Soheila Shahmohammadi³

¹Diabetes Research Center, Mazandaran University of Medical Sciences, Sari, IR Iran

²Faculty of Medicine, Mazandaran University of Medical Sciences, Sari, IR Iran

³Mazandaran Pediatric Infectious diseases Research Center (MPIDRC), Mazandaran University of Medical Sciences, Sari, IR Iran

*Corresponding author: Daniel Zamanfar, Diabetes Research Center, Mazandaran University of Medical Sciences, Sari, IR Iran. Tel: +98-1133344506, Fax: +98-1133344506, E-mail: danielzamanfar@gmail.com

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Introduction: Allgrove's syndrome (AS) is a rare cause of adrenal insufficiency inherited in an autosomal recessive pattern. Usually the disease is manifested during the first decade of life with severe hypoglycaemia, which can lead to sudden death.

Case Presentation: Here we described two cases of Allgrove's syndrome; the first case was an 8-year-old male admitted to hospital for evaluation of seizure and gait abnormality and the second case was a 4-year-old boy admitted for evaluation of hyperpigmentation of his skin and buccal mucosa for eight months, also we made a review of literature.

Conclusions: Alacrima is considered to be the earliest clinical manifestation of Triple A syndrome and early recognition of glucocorticoid deficiency would prevent hypoglycaemic convulsions, neurological sequelae and death. A careful replacement of glucocorticoids is critical to avoid adrenal crisis and allow normal growth and development.

Keywords: Syndrome; Adrenal Insufficiency; Alacrima; Case Report

1. Introduction

Allgrove's syndrome characterized by insensitivity to adrenocortico trophic hormone (ACTH), was first described by Allgrove et al. in 1978 and consists of a triad of achalasia cardia, alacrima and adrenal hypoplasia (1). Gazarian et al. (2), in 1995 called it as 4A syndrome, due to its variable association with autonomic and neurological manifestations (3, 4).

General manifestations of this syndrome include isolated glucocorticoid failure, hypoglycemia, weakness, fatigue, anorexia, nausea, vomiting, constipation abdominal pain, diarrhea, salt craving, postural dizziness, weight loss, hypotension, hyperpigmentation, vitiligo, auricular calcification, electrolyte disturbances, anemia, eosinophilia, hypothyroidism, alacrima and achalasia (1, 5-7).

Other manifestations include palmoplantar hyperkeratosis, short stature, gonadal failure, microcephaly, osteoporosis and pes cavus, neurological abnormalities including autonomic, sensory and motor neuropathies, progressive spastic tetraparesis, dysarthria, dysphagia, prolonged nerve conduction, muscle weakness, distal limb atrophy, deafness, mild mental retardation, optic atrophy, mild dementia and cerebellar ataxia (8-13).

This syndrome is unresponsive to ACTH, because several mutations have been reported in ACTH receptor genes. However, the apparently normal ACTH receptor gene in affected children suggests that the etiology of AS is probably heterogeneous (14). Here, we highlighted the importance of hypoglycaemia, hyperpigmenta-

tion and alacrima as some clues in the diagnosis of Allgrove's syndrome.

2. Case Presentation

2.1. Case Report 1

An 8-year-old boy born following a preterm pregnancy was the first child of a consanguineously married couple. His younger sister was healthy. Since birth, he had cry without tears, but no sign of eye discomfort. He started to crawl at 9 months and walked when he reached 15 months. The patient remained well until the age of three years when he had hypoglycemic seizure attacks. He had developing progressive vomiting and abdominal pain and weight loss. At the same time, barium swallow study showed achalasia. At age of five years, he was referred to pediatric department at Bou Ali Sina hospital in Sari, Iran. The patient was admitted due to seizure and generalized pigmentation, especially on his knee, elbows and buccal region. The blood sugar level was 20 mg/dL and EEG showed generalized spikes at the time. He received Phenobarbital 60 mg daily for eight months followed by Sodium Valproate 600 mg daily. Biochemical studies had normal findings. The blood pressure was 100/70 mmHg on his right arm and 90/70 mmHg on his left arm. Fasting blood cortisol level was (149.5 nmol/L) (normal range, 138 - 635). Blood ACTH level was (1397 pq/mL) (normal,

7.2 - 63.3). Free Thyroxin level was 15.82 pq/mL (normal, 8 - 20) and TSH 5.1 mlu/mL (normal, 0.3 - 5.0). In physical examination, height and weight were on 75 and 25 centile, respectively. There were no dysmorphic features, but the lower limbs were in valgus position with clumsy gait. There was proximal muscle weakness and wasting of tight muscle with brisk reflexes in both feet. The patient had sparse hair, used glasses and staring. The patient received steroid replacement therapy with oral hydrocortisone. Following steroid replacement therapy, seizures attacks stopped and significant improvements occurred in muscle weakness and hyperpigmentation after one year. During 3.5 years follow-up, he showed impressive improvement as able to perform his daily routines by himself without support.

2.2. Case Report 2

A 4-year-old boy born following a full-term pregnancy and the third (also the last) child of a consanguineously and healthy married couple was admitted. His brother and sister were healthy. He was admitted for evaluation of hyperpigmentation of skin and buccal mucosa since 8 months ago. Moreover, since one year ago, he had developed dysphasia due to achalasia, which was more for solids and associated with abdominal pain and vomiting. The patient had alacrima since birth. He had tic movement and neurologic development delay in speech and movements. He had been able to speak completely since 8 months ago, he could not walk lonely. He had no history of seizure or recurrent infection. The patient had Neurodevelopmental delay (NDD), muscle wasting, mental retardation and poor pupil reflex at admission. He had a history of cyanosis and NDD before admission, which necessitated assessing methemoglobinemia, metabolic disorders and neurological deficits (Brain MRI). None of these assessments showed significant diagnostic findings.

Physical examination revealed BP: 95/60 (50%), PR: 100/min, RR: 24/min, TA: 37°C, weight: 14 kg (25%), height: 112 cm (97%), head circumference (HC): 47.5 cm (5% - 10%). The patient had enlarged face and hyperpigmentation of whole body, especially in lips and buccal mucosa.

In external genitalia area, penis was normal in size, but the testes were not descended. Dimpling in about 3 cm of anus was observed. In neurological examination, normal cutaneous sensation, normal deep tendon reflex (DTR), muscle wasting and clumsy gait were observed.

Hematologic examinations were as follows; WBC: 6800 (PMN: 28%, Lymph: 71%), Hb:11.1, Hct: 32.8, MCV: 74, MCH: 25, Plt: 262000, HbF: < 0.5, Hb A1: 97%, Hb A2: 3%, and Met Hemoglobin:1.6, Serum IgA, IgE and Anti endomysial IgA: NI, Ani TTG IgA and Anti TTG IgG: NL, T4:8, TSH:3.5, Amoniac, Lactat and other metabolic testes: NI, Echocardiography: NL, Brain MRI:NL, EEG:NL, FBS:87, Na:135, K: 4.2, Cortisol 8 Am: < 0.15 L, (6 - 10), 17 OH- Progesterone: 0.3 (0 - 0.82), ACTH: > 1500 H (4.7 - 48).

Ophthalmologic examination showed a mild dry eye

and poor pupil reflex. For neurologic examination, electromyogram-nerve conduction velocity (EMG-NCV) was suggested. Gastrointestinal consultation and barium meal study were performed.

Differential diagnoses were adrenal insufficiency, adrenal hypoplasia, familial glucocorticoid deficiency (FGD) and Allgrove syndrome.

After confirmation of the diagnosis, medical therapy was started and he referred to pediatric gastroenterology center for therapeutic goals. The current status of patient is fine and could eat solid food for the first time.

3. Discussion

Allgrove syndrome or Triple A syndrome (AS; MIM 231550) is an autosomal recessive disorder associated with adrenal insufficiency, alacrima and achalasia, which was first described in 1978 by Allgrove et al. (1, 15). The incidence of this syndrome is unknown and only scarce reports exist in the literature. Adrenal insufficiency is characterized by insensitivity to adrenocortico trophic hormone (ACTH). In most patients with isolated deficiency of glucocorticoid, elevated levels of ACTH and normal aldosterone production exist. Nonetheless, in about 15% mineralocorticoid production may be impaired later (16, 17). Often patient presents with potentially episode of fatal hypoglycaemia. In this syndrome, there are autonomic neurological abnormalities associated with three other symptoms including alacrima, achalasia and adrenal insufficiency named as 4S syndrome (18).

The diagnosis of AS should not be excluded despite lack of adrenal insufficiency. There are several evidences of cases indicating classical symptoms of primary adrenal insufficiency such as hypoglycaemia symptoms and shock. In skin examination, hyperpigmentation may be observed, and presence of pigmentation changes in the buccal mucosa, loop areas and scar tissues should be carefully examined. Absence of hyperpotassemia does not necessarily exclude the diagnosis of adrenal insufficiency in the presence of infection. Hypotension can be observed both in infection-related sepsis and adrenal insufficiency. It has been claimed that a random cortisol measurement below 15 µg/dL is sufficient to diagnose adrenal insufficiency, while others believed that the level should be below 25 µg/dL. According to another opinion, a cortisol increment < 9 µg/dL after cosyntropin stimulation is adequate for making a diagnosis of adrenal insufficiency (19).

Other known cause of ACTH insensitivity is familial glucocorticoids deficiency (FGD), which has adrenal insufficiency as sole manifestation. AS was initially considered a variant of FGD since ACTH insensitivity was common in both disorders. Plasma epinephrine concentration is extremely low in patients with isolated familial glucocorticoid deficiency, which may cause low resting systolic blood pressure and postural hypotension and contribute to fasting hypoglycaemia (5, 17). However, data from re-

cent studies suggest that AS is in fact a distinct entity as gene for this syndrome maps to the chromosome 12q13 near type keratin gene (17, 20, 21), unlike that of FGD found on chromosome 18p11.2 (22). In addition, mutations in ACTH receptor gene have been found in patients with AS. Recent studies implicate mutation in the AAAS gene, which codes for WD repeat protein termed ALADIN, resulting in expression of a truncated protein suggesting loss of function (23). The ALADIN gene is a 60-KD protein with a 170-AA Domine composed of 4WD repeats.

However, the specific function of ALADIN is unknown, because WD-repeat proteins play a role in many cellular processes. A large number of mutations identified in patients with Allgrove syndrome including nonsense, frame shift or splice-site mutations as predicted to truncate the C terminus of ALADIN, suggesting that this domain is important for the function of ALADIN. Furthermore, four point mutations exist, which three of them (H160R, S263P and V313A) are within the WD-repeat domain, whereas the fourth (Q15K) is close to the N terminus. No obvious correlation has been found between different ALADIN mutations and disease phenotype. Other factors play an important role in the pathogenesis of triple A syndrome. In a proteomic analysis of mammalian nuclear pore complexes (NPCs), it has been identified that ALADIN is a protein that biochemically fractionates with and localizes to NPCs. NPCs as large, multiprotein complexes span the nuclear envelope (NE) by forming a selective channel between the cytoplasm and nucleus. NPCs play a role in a variety of cellular processes, including cell-cycle progression, control of gene expression and signal transduction.

ALADIN could be involved in any of these aspects of NPC function such as mediating the assembly of subdomains of the NPC or nucleating the formation of transport complexes. Identification of ALADIN as a component of NPCs facilitated a more detailed analysis of the molecular basis of mutations causing the disease. It has been declared that characterization of an ALADIN mutant cell line indicates that the absence of functional ALADIN cannot produce morphological abnormalities in nuclei, NPCs or NEs, indicating that the defect is functional rather than structural (18).

Variable manifestation of the disorder suggests that the syndrome might be due to a contiguous gene deletion (3, 10). However, in several consanguineous families of European descent and in four Puerto Rican families with no identified consanguinity, AS was mapped to 12q13 by linkage analysis (11, 12). In these kindreds, genetic analysis did not suggest the presence of microdeletions. Searching for gene responsible for AS, a variety of genes were excluded in the 0.5-cM interval between polymorphic markers D12S361 and D12S368 (13, 14). The gene coding for the neuronal sodium channel SCN8A had been previously mapped to a clone containing D12S368 (16), placing it at the AS locus. SCN8A is widely expressed in brain and spinal cord and in the

peripheral nervous system (20). Furthermore, three allelic mutations of SCN8A in mouse cause a variety of neurologic abnormalities, including paresis, paralysis, ataxia, tremor and dystonia (22). However, haplotype analysis placed the SCN8A gene telomeric to the AS candidate region (15).

The symptoms vary at the time of presentation. There are also high variability in severity and age of presentation. In addition, it is often progressive (18). The time of adrenal insufficiency varies. It does not occur immediately after birth, but results from progressive process leading to hypo-function of adrenal gland at variable time after birth (4, 16), although preservation of cortisol secretion up to the third decade of life has been reported (21, 24).

Neurological abnormalities include autonomic, sensory and motor neuropathies, progressive spastic tetraparesis, dysarthria, dysphagia, prolonged nerve conduction times, muscle weakness, distal limb atrophy, deafness, mild mental retardation, optic atrophy, anisocoria, periventricular brain heterotopias, mild dementia and cerebellar ataxia. Accumulated evidence shows that triple-A syndrome is caused by abnormal development of the autonomic nervous system. This syndrome has clinical similarities with amyotrophic lateral sclerosis (25).

Muscle hypotonia, muscle weakness, progressive distal muscular atrophy, pes cavus, loss of deep, sensibility and other sensory impairments have been addressed. About 30% of all patients have autonomic impairment (17). In about 20% of all patients, dermatologic abnormalities are present including hyperkeratosis of palms and soles with fine palmar creases. Other manifestations are significant short stature, microcephaly, osteoporosis, lack of eyelashes, dysmorphic facies with long narrow face, long philtrum, down-turned mouth, thin upper lip, poor wound healing, scoliosis, long QT syndrome and type IIb hyperlipoproteinemia (15, 17).

Alacrima is considered the earliest clinical manifestation of Triple A syndrome as a progressive disorder and appears during early infancy, which can take years to develop into a full-blown clinical picture, but is often ignored by parents (5, 6, 19, 26). However, there are no available data, based on current knowledge, about the exact ocular surface features, which may guide appropriate diagnosis and treatment in a clinical setting (26). Patients with triple-A syndrome present with ophthalmic manifestations other than alacrima. For example, Brooks et al. introduced a 12 year-old female patient with triple-A syndrome with decreased tear production, no spontaneous tearing, inappropriate accommodation and superficial punctate keratopathy, which needed frequent ocular lubrication (27). Alacrima was observed in our patients and mothers noticed that their babies cry without tears since birth.

Achalasia is a devastating problem of triple-A syndrome mostly appears in patients aged 6 months to 16 years. It

presents with symptoms of dysphagia, vomiting, weight loss and irritability (6). Pedreira reported a 37 year-old patient with triple-A syndrome with achalasia presented 20 years before their diagnosis (2). This delayed diagnosis must emphasize the importance of careful physician assessment of adrenal function in patients with alacrima and achalasia symptoms (28). Achalasia occurs in about 75% of all cases; although, in one rare report, the age onset of symptoms was in 3 month-old siblings (6, 7). In fact, achalasia and gastric atonia cause recurrent or chronic pulmonary disease due to aspiration. For this reason, achalasia can be a predominant feature of this syndrome (4, 17, 19, 28, 29). Nevertheless, oesophageal achalasia is uncommon in children. Absence of peristalsis within the body of the oesophagus is detected by a defect in relaxation of the gastro-oesophageal sphincter and a dilatation in the proximal oesophagus. Achalasia may sometimes be a part of AS and displays autosomal recessive inheritance disorder (2, 8, 14). Esophagography of the patient showed a narrowing in the cardio-oesophageal junction and a dilatation of the oesophagus proximal to the junction (19). The etiology of achalasia is unknown, but might be due to degeneration of autonomic plexus. In our patients, achalasia occurred in less than 4 years of age. At the same time, neurological features appeared and found to be progressive in nature. The first case had upper muscle weakness and ataxia and brisk reflexes. It is important to keep a high index of suspicion and look for all possible causes in every patient presenting with hypoglycemia. Features like hyperpigmentation and alacrima could lead to diagnosis of unsuspected diseases as in these cases. Triple-A syndrome can also present in adulthood. Manifestations of the disease in adults are the signs and symptoms of adrenocortical insufficiency such as hypoglycemia, weakness, fatigue, anorexia, nausea, vomiting, postural dizziness, weight loss, hypotension, hyperpigmentation, electrolyte disturbance, achalasia and alacrima. Other clinical manifestations are palmo-plantar hyperkeratosis, gonadal failure and short stature. Conversely, in adults, neurologic abnormalities are more common including autonomic, sensory and motor neuropathies, dysarthria, progressive spastic tetraplegia, distal limb atrophy, deafness, mild mental retardation, optic atrophy and cerebellar ataxia (27). Specific facial characteristics can be seen in some patients including a long thin face, long philtrum, microcephaly and down turned mouth with narrow upper lip (10). Each patient with achalasia or adrenocortical insufficiency must be assessed periodically for gastrointestinal, adrenocortical and neurological involvements, in particular autonomic abnormalities. Patients should be assessed regarding alacrima confirmed by an ophthalmologic examination (27, 30).

Alacrima is considered the earliest clinical manifestation of Triple A syndrome and early recognition of glucocorticoid deficiency would prevent hypoglycaemic convulsions, neurological sequelae and death. A careful replacement of glucocorticoids is critical to avoid adrenal crisis and allow normal growth and development.

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