
Case Report

NEUROLOGICAL MANIFESTATIONS OF ALLGROVE SYNDROME

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Allgrove syndrome is a rare syndrome with conspicuous neurological abnormalities. We describe a 16-year-old male with Allgrove syndrome suffering from upper and lower motor neuron diseases, autonomic dysfunction, muscle weakness, seizure, optic atrophy, ataxia, and peripheral demyelinating polyneuropathy primarily involving distal lower limbs. Since 3 years of age, he had experienced frequent hospital admissions for convulsion, hypoglycemia, dysphagia, intractable vomiting, loss of consciousness, treatment of achalasia, and suspicious seizure. His younger sister had died at the age of 3 with no diagnosis. Early treatments with corticosteroids dramatically improved his signs and symptoms.

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Introduction

Allgrove syndrome (AS), also known as triple-A syndrome (alacrima, achalasia, and adrenal insufficiency) is a rare autosomal recessive disease that has been mapped to chromosome 12q13.¹⁻³ It was first introduced by Allgrove in 1978.² 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, 2, 4, 5} Other manifestations consist of palmoplantar hyperkeratosis, short stature, gonadal failure, microcephaly, osteoporosis, and pes cavus. Neurological abnormalities comprise 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.⁶⁻¹¹ Accumulated evidence indicates that triple-A syndrome results from abnormal development of the autonomic nervous system. It bears clinical similarities with amyotrophic lateral sclerosis.⁴ This syndrome is unresponsive to ACTH because several kinds of mutations in the ACTH receptor genes have been reported.¹² However, the apparently normal ACTH receptor gene in affected children suggest that the etiology of AS is probably heterogeneous.¹² Achalasia is very uncommon in children. It is still more uncommon when associated with alacrima and adrenal insufficiency.⁶ Here, we describe a 16-year-old male who was admitted to hospital for evaluation of seizure and gait abnormality, and was finally diagnosed as AS. To the best of our knowledge, this is the first report of AS in Iran.

Case Report

The patient was born following a full-term pregnancy. He was the child of healthy parents and his younger sister had suddenly died at 3 years of age without any definitive diagnosis. He started to crawl at 9 and walked at 15 months. His speech was understood only by his mother because of his

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Figure 1. Increased pigmentation of skin, deformation and atrophy of limbs muscles, and atrophy of facial muscles.

nasal speech and dysarthria.

He remained well until 3 years of age when he started to develop progressive vomiting, dysphagia, abdominal pain, and weight loss. At the age of 3, he developed generalized pigmentation especially on his knees, elbows, the scar of operation, and buccal region.

At the age of five, he was referred to Dr. Ahari Children's Hospital in Tehran where a barium swallow showed some tertiary wave activity and achalasia. Myotomy was performed when he was 6 years old and partially improved his vomiting and dysphagia. CT scan of the brain, electromyography (EMG), and nerve conduction study were normal at that time.

He was admitted to hospital several times for weakness and hypoglycemia. At the age of 15, he experienced a generalized tonic-clonic seizure. His blood sugar was 20 mg/dL and EEG showed

generalized spikes at that time. He received phenobarbital 60 mg daily for 6 months followed by sodium valproate 600 mg daily. He started to become drowsy and floppy, and consequently he received sodium valproate 400 mg daily for 3 months. After one month, he became so weak that he was not able to walk without support. Chest X-ray showed low bone density and a calcified lymph node in the right axillary region. Biochemical studies were normal. His blood pressure was 80/50 mmHg on his right arm and 70/50 mmHg on the left. Fasting blood cortisol was 0.49 µg/dL (normal range, 5.5 to 23 µg/dL). The blood cortisol level was 0.6 µg/dL 24 hours after ACTH stimulation.

Total thyroxine was 3.2 µg/dL (normal range, 4 to 12 µg/dL); T₃, 85 ng/dL (normal range, 70 to 200 ng/dL); and TSH, 5.1 µIU/mL (normal range, 0.3 to 5 µIU/mL). On physical examination, he looked a very slim 16-year-old boy with dark skin except for palmar and plantar surfaces. Other manifestations were bilateral ptosis more evident on the right side, optic atrophy, atrophy and fasciculation of the tongue, and atrophy and weakness of the facial muscles. Other muscles especially thenar and hypothenar muscles were weak and atrophic also. Deep tendon reflexes were increased in all four limbs. He had swan-neck deformity of fingers and plantar reflexes were extended without clonus. He also had cubitus valgus, pes planus, genu valgum, and cutis anserine (Figure 1). Joint motions were limited because of muscle contractures. Pain, thermal, and proprioceptive perceptions were normal. He had experienced an unstable mood and deficient tear production since early infancy. His spastic tetraparesis had progressed with mild ataxia. EMG and nerve conduction studies showed decreased nerve conduction velocity in the tibial, median, and ulnar nerves with prolonged distal latencies and no evidence of myopathy. Brain MRI was normal. He was given prednisone, 10 mg daily, and his symptoms and signs improved so that he could ride his bike after 2 weeks.

Discussion

Neurological manifestations of AS are not well described in the literature and many have reported only some of them. It is a rare cause of congenital adrenal insufficiency due to ACTH hormone resistance.¹²

Histological examination of the adrenals reveals

pronounced atrophy of the cortical zona fasciculata and reticularis. The zona glomerulosa and adrenal medulla are normal. Mineralocorticoid function is usually normal though Werder et al found a suboptimum aldosterone response in one of their patients.^{2, 13, 14} The condition has been mapped to chromosome 12q13 in a maximum interval of 6 CM between loci D12S1629 and D12S312.¹⁵ Link analysis in 12 triple-A families mostly originating from North Africa confirmed that the disease maps to the 12q13 region and suggested that triple-A is a genetically homogeneous disorder. The expression of this gene in both neuroendocrine and cerebral structures points to a role in the normal development of the peripheral and central nervous systems.³ We assume that the association of these three uncommon conditions cannot be incidental. The exact cause of achalasia is not known but it is thought to be due to a disturbance of the esophageal autonomic plexus with degeneration of the nerve fibers.² These nerves do not depend on acetylcholine or adrenaline as transmitters but are rich in ATD which may act as neurotransmitter.² There is some evidence that cyclic AMP is involved in the action of corticotropin and it is likely that the abnormalities in our patients could result from disturbances of ATP/cyclic AMP metabolism or binding in both the adrenal gland and the esophagus.² Adrenoleukodystrophy in combination with Addison's disease, originally included under the rubric of Schilder's disease, is transmitted as an X-linked recessive trait with an incidence of 1 in 20,000 male births.¹ In typical cases, massive degeneration of the myelin occurs, often asymmetrically, in various parts of the cerebrum, brainstem, optic nerves, and sometimes in the spinal cord. Degradation products of myelin are visible in macrophages in the recent lesions namely, sudanophilic demyelination. Axis cylinders are damaged but to a lesser degree.¹ Our patient might have a similar metabolic disorder which would have lead to degeneration of the myelinated and unmyelinated nerves leading to autonomic symptoms such as achalasia and defective lacrimation. Adrenal replacement therapy prolongs life and occasionally leads to a partial neurologic remission. A diet enriched with monosaturated fatty acids and devoid of long-chain

fatty acids appears to slow the progression of the disease.¹

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