Turkish Journal of Endocrinology and Metabolism, (2004) 2 : 81-83 **CASE REPORT**

Autonomic Dysfunction in the Adrenal Insufficiency/Alacrima/Achalasia (Triple A) Syndrome (Is it Quaternary A Syndrome?)

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Allgrove or Triple A Syndrome (AS) is an autosomal recessive condition associated with adrenal insufficiency due to ACTH resistance, alacrima, and achalasia. Other features of AS include autonomic and/or peripheral neuropathy, hyperkeratosis and delayed wound healing, mental retardation and dementia, and rarely, short stature. To increase awareness about the frequent autonomic nervous system involvement we want to report a child with 3A syndrome who later developed distal polyneuropathy in lower extremities.

Key words: 3A syndrome, autonomic dysfunction

Introduction

Allgrove or Triple A Syndrome (AS) is an autosomal recessive condition associated with adrenal insufficiency due to ACTH resistance, alacrima, and achalasia. Allgrove et al. First described it in 1978. Other features of AS include autonomic and/or peripheral neuropathy, hyperkeratosis and delayed wound healing, mental retardation and dementia, and rarely, short stature (1-12). In 1995 Gazarian et al proposed the name ‘‘4 A syndrome’’ for this same disorder, to increase awareness about the frequent autonomic nervous system involvement (2).

We report a child with 3A syndrome who later developed distal polyneuropathy evident in lower extremities.

Patient Report

A 11 (6/12) year-old girl was admitted to the hospital with a history of darkening her skin colour for two years. She also had fatigue, weakness and abdominal tenderness. She was the 5th child of non-consanguineous healthy parents. The first child of the family had died instantly when she was 11 years old. She also had hyperpigmentation for 3 years but she never had been admitted to the hospital. The other 5 children are healthy and they don’t have any problems since now. There was no positive family history except her sibling. On physical examination she was 138 cm (HSDS: -1,85), and weighed 30,5 kg (WSDS= -1.65). Her blood pressure was 120/70 mm/Hg, pulse rate was 72/min and respiratory rate was 21/min. Her skin was dry with hyperpigmentation especially at the upper part of her body, and over the knuckles of the hands and at the base of the toenails. She had Grade Ia goiter, P1 pubarche and T1 telarche. The remainder of the physical examination was unremarkable.

Laboratory examination showed: ACTH: 1250 and 1500 pg/ml (normal: 5-50 pg/ml), Cortisol: 13,2 μgr/dl (normal: 5-25 μgr/dl), 17OHP: 1,4 ng/ml (normal: 0,31-2,17 ng/ml), DHEA/S: 48,5 μg/dl (normal: 100-300 μg/dl), plasma renin activity: 1,8 ng/ml/hr (normal: 1,9-6 ng/ml/hr), aldosterone: 18,3ng/dl (normal: 3-35.5 ng/dl), PTH 18 μgr/L (normal: 7-73 μgr/L), AntiTPO: 2,9 IU/ml (normal 0-50 IU/ml), fasting blood glucose: 60 mg/dl, Na: 140 meq/L, K:3.9 meq/L, CPK: 115 U/L, Ca: 10.2

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mg/dl, P: 5.36 mg/dl, alkaline phosphatase: 324 U/L. After ACTH stimulation test, peak 17OHP and peak cortisol were 2,5 ng/ml and 18,2 µgr/dl respectively. Abdominal ultrasonography, Brain magnetic resonance imaging (MRI) and adrenal MRI were normal. Orbital CT scan revealed absent lacrimal gland tissue at the right side.

After treatment with hydrocortisone (15 mg/m^2/day), the patient's hyperpigmentation disappeared. About one year later, she began to complain about recurrent episodes of dysphagia. After detailed investigation it was learned that she also had diminished tear production. Schirmer test was positive (<2 mm for each eye after 5 minutes). Upper gastrointestinal barium swallow X-ray series showed that the passage in gastroesophegeal junction was not continuous and there was dilatation at the upper part of the esophagus. After 6 months the X-ray studies were repeated and typical signs of achalasia were seen (the terminal part of the esophagus showed a beaklike narrowing). Omeprazole and artificial tears were added to the treatment.

For suspected neurological dysfunctions detailed neurological examination and electromyography was performed. On neurological examination; gag reflex was normal, the other cranial nerves were intact, tendon stretch reflexes were preserved, fundoscopic findings were normal. There was no sensory impairment but papillary atrophy was seen on the tongue. By needle electromyography diffuse loss of motor units were observed and it was more severe distally than proximally, particularly in the lower limbs. Intradermal histamine test was normal.

Discussion

The syndrome of adrenocortical insufficiency, alacrima, and achalasia has been described in the past 24 years. These symptoms vary in the time and course of presentation are accompanied later by slowly progressive multisystemic neurologic deterioration. Neurologic features of this syndrome include a mixed pattern of upper and lower neuron dysfunction. Gazarian et al. (1995) and Persic et al (2001) proposed the name ''4A Syndrome'' instead of ''3A Syndrome'' to increase the awareness about this frequent nervous system involvement (2,3).

In a review of 20 cases, evidence of cortisol deficiency was present in all cases based on clinical and laboratory findings, with symptoms of adrenal insufficiency beginning between the ages of 1.0 and 8.3 years (4). However, in our patient, symptoms of adrenal insufficiency began in late childhood period when she was 11.5 years old. The endocrine studies disclosed a compensated adrenal insufficiency, with subnormal serum morning/ fasting cortisol (13,2 µgr/dl; normal, 5-25µgr/dl), but with very high serum adrenocorticotropic hormone (ACTH) level (1250/1500 pg/ml; normal 9-52 pg/ml). Values of serum aldosterone (18,3 ng/ml; normal:4-31 ng/ml), and renin activity (1,8 ng/ml/hr; normal 1,5-5,7 ng/ml/hr) were in normal ranges and there was no mineralocorticoid deficiency though some cases have been reported to have mineralocorticoid deficiency (5-6).

Alacrima, which appears to be the most consistent early finding of 3A Syndrome is most likely a manifestation of an underlying autonomic neuropathy (7). It is mostly seen in early infancy but our patient had the symptoms about the same time of the diagnosis and she required 'artificial tears' to avoid discomfort. Orbital CT scan revealed absent lacrimal gland tissue at the right side. The patient and her parents insisted on that she had tears in early childhood period but probably it was from the left side or they couldn't recognize alacrima.

Achalasia has a variable age of presentation (2-17years) but other neurological abnormalities generally occur later (8). Rarely the diagnosis of achalasia is made before the diagnosis of cortisol deficiency (9). The etiology 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 (4,9). The esophagus and lower esophageal sphincter contain receptors for numerous neurohumoral and hormonal factors and, like the lacrimal glands, are under parasympathetic and sympathetic efferent nervous control (9). In our patient, though, the first sign of achalasia began after one year of diagnosis, the definite diagnosis was 6 months later.

Some cases of 3A Syndrome involves the peripheral motor and sensory fibers, pyramidal tract, motor coordination systems, optic nerve, speech, basal ganglia, cognitive function, skin, and osseous development (2,4,8). Peripheral neuropathy has occasionally been noted, but is poorly characterized as sensory motor neuropathy, predominantly motor neuropathy, or sensory neuropathy, possible with

demyelinative features. By neurological examination, our patient's; cranial nerves were intact, tendon stretch reflexes were normoactive and fundoscopic findings were normal. There was no sensory impairment but papillary atrophy was seen on the tongue. By needle electromyography diffuse loss of motor units were observed and it was more significant distally than proximally, particularly in the lower limbs. As there are many known similarities between the enteric and central nervous system it seems very likely that the alacrima, autonomic dysfunction, and abnormalities of the central nervous system have an origin in common with the achalasia that is caused by a denervating process. Our patient showed normal response to intradermal histamine unlike patients with familial dysautonomia. Similarly, plasma levels of very long-chain fatty acids were not elevated as seen in adrenoleukodystrophy.

Here, our purpose is to increase awareness of autonomic nervous system involvement in 3A Syndrome. May be its better to rename the disease as 4A Syndrome as Gazarian et al proposed.

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