



Triple A Syndrome: A Case Report

Triple A Sendromu: Olgu Sunumu

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Abstract

Triple A syndrome is a rarely seen autosomal recessive disease characterized by achalasia, adrenal failure and alacrima. The syndrome is frequently seen in childhood. The appearance of its components are usually ordered as alacrima, achalasia and adrenal failure. The majority of the patients diagnosed in the later stages predominantly present with neurological symptoms. In this study, a 21-year-old male who was referred to our clinic with clinical findings of chronic adrenal failure and was diagnosed WITH triple A syndrome is presented. This patient had been operated three years ago due to achalasia. The diagnosis and treatment of adrenal failure in this syndrome is the most important determinant and indicator in the prognosis of the disease. *Turk Jem 2014; 18: 97-99*

Key words: Alacrima, adrenal failure, neuropathy

Özet

Triple A sendromu akalazya, adrenal yetmezlik ve alakrimia ile karakterize otozomal resesif geçiş gösteren, nadir görülen bir hastalıktır. Sendrom sıklıkla çocukluk çağında görülmektedir. Sendromun komponentlerinin çıkış sırası genellikle alakrimia, akalazya ve adrenal yetmezlik şeklindedir. Geç tanı konulan hastaların çoğu baskın bir şekilde nörolojik semptomlarla prezente olur. Burada 21 yaşında kronik adrenal yetmezlik kliniği ile başvuran ve Triple A sendromu tanısı konulan bir erkek olgu sunuldu. Olgu 3 yıl önce akalazya nedeni ile opere olmuştu. Bu sendromda adrenal yetmezliğin tanı ve tedavisi hastalığın prognozunda en önemli belirleyicidir. *Turk Jem 2014; 18: 97-99*

Anahtar kelimeler: Alakrimia, adrenal yetmezlik, nöropati

Introduction

Triple A syndrome or Allgrove syndrome was first identified by J. Allgrove in 1978 (1). The major components of the this disease which has a hereditarily autosomal recessive character and a pattern of multisystemic involvement are achalasia, alacrima and adrenal failure. This syndrome develops due to mutations in the Achalasia-Addisonism-Alacrima syndrome (AAAS) on chromosome 12q13 encoding the nuclear pore protein ALADIN (2,3). The clinical pattern is often accompanied by findings of autonomous nervous system involvement, and therefore, it is sometimes named as 4 A syndrome (4). Triple A syndrome is usually diagnosed in infancy and childhood. Here, we present a 21-year-old patient diagnosed to have triple A syndrome and manifesting neurological findings.

Case Report

A 21-year-old male was admitted to our clinic with the complaints of nausea, vomiting, anorexia, abdominal pain, weight loss,

rashes and darkening of the skin. A weight loss of up to 10 kg had occurred in the last 6 months. Darkening of the skin developed especially on the palms as well as inside the mouth and the gums. Further investigation revealed that the patient had complaints of dysphagia 3 years ago and underwent Heller myotomy following the diagnosis of achalasia. There was no geneological kinship between the mother and father. He had 7 healthy siblings. However, his family history revealed that two sisters had died at the age 23 and 25 years after the complaints of dysphagia, weight loss and darkening of the skin. Physical examination revealed a blood pressure of 90/50 mmHg, pulse of 80 bpm, and body temperature of 36.8 °C. Increased pigmentation was observed in his skin and mucosa. There was no palmoplantar hyperkeratosis. Clinical examination revealed no findings of hepatosplenomegaly. Cardiovascular and respiratory system were also observed to be normal. Pes cavus deformity was observed in both of his feet. In the neurological examination, no Achilles reflex could be observed, his other deep tendon reflexes were observed to be normoactive. The dorsiflexion power of both feet was found to be 0/5. The abduction and adduction strength

of both hands was 4/5. Atrophy of the thenar and hypothenar muscles was observed. There was no sensorial defect. The other neurological examinations were found to be normal. Hemogram revealed a normochromic normocytic anemia (hemoglobin:12g/dl, mean erythrocyte volume: 83 fl). The electrolyte levels and biochemical analyses were normal. Basal cortisol and ACTH levels were found to be 3.1 ug/dl and 1200 pg/ml, respectively in our patient who was suspected to have adrenal insufficiency due to the clinical presentations. Standard 250 µg cosyntropin stimulation test was performed in order to detect adrenal failure, and maximum cortisol response was observed to be 3.5 µg/dl. The potassium level in our patient who was diagnosed to have adrenal failure was found to be 4.5 mmol/L. He was not considered to have mineralocorticoid deficiency, therefore, daily hydrocortisone replacement was at 20 mg/day. Since the patient had a history of surgery due to achalasia, he was thought to have triple A syndrome. Schirmer's test was done for alacrima which is another component of the syndrome and it was found to be positive (3 mm in both eyes after 5 minutes). The diagnosis of triple A syndrome was established. Electromyography demonstrated slowing of both ulnars, median, peroneal and posterior tibial motor neural conduction velocities and lower compound action potentials. Sensory nerve conduction velocity was normal. F response (a late response in EMG as a result of supramaximal stimulation of a peripheral nerve) could not be obtained in some nerves, whereas there was prolongation of the distal latency and reduced persistence. These findings showed a relevance with distal symmetrical peripheral neuropathy. There was no parasympathetic autonomic disorder in electrophysiological heart rate variability test. The patient was examined for sympathetic autonomic neuropathy; orthostatic hypotension was observed.

Discussion

Triple A syndrome is a hereditary autosomal recessive disease with multisystemic involvement and accompanied by achalasia, alacrima, adrenal failure, and neurological findings. This syndrome manifests itself in the first decade of life. Alacrima is usually the earliest and the most persistent finding (5,6). However, it is not a common presenting complaint (7). Alacrima is associated with structural abnormalities in the lacrimal glands as well as autonomic dysregulation (8). Mullaney et al. reported that the lacrimal glands were found to be reduced in size and the number of serous secreting cells were found to be decreased in the lacrimal gland biopsy of 3 cases with triple A syndrome (9). The other manifestations apart from alacrima are keratoconjunctivitis sicca, corneal ulcer, pupillary abnormalities, accommodation disorder and optic atrophy (10). Diagnosis of alacrima can be made by Schirmer's test (7). In our case, the diagnosis of alacrima was made at 21 years of age, however, the patient had a complaints of dryness and feeling of sinking in the eyes for more than ten years. The other ophthalmologic problems identified in the literature were not found.

ACTH resistance is considered to be another component of triple A syndrome; and adrenal failure in this syndrome is diagnosed in the first decade of life with frequent hypoglycemic seizures

and shock (8). The non-existence of adrenal hypofunction in the early post-natal period brings to the mind a gradual developing adrenal destruction and degeneration (11). The number of reported cases of adrenal failure in adolescence is quite rare in literature (12,13). Our case was referred to the clinic with symptoms, such as nausea, vomiting, weight loss, abdominal pain, darkening in the skin and mucosa, and adrenal failure. The examinations done for investigating adrenal failure showed basal cortisol level of 3.1 ug/dl and standard 250 µg cosyntropin stimulation test demonstrated maximum cortisol response of 3.5 µg/dl. The patient in whom ACTH level was measured as 1200 pg/ml was diagnosed to have adrenal failure based on the clinical findings and laboratory analyses. The potassium and bicarbonate levels in our case at the time of referral to the clinic were found to be normal; mineralocorticoid deficiency was not considered. Mineralocorticoid deficiency can develop in 15% of patients with triple A syndrome after the diagnosis (8). The first clinical presentation of the syndrome in our case was achalasia. In this syndrome, achalasia may develop due to a decrease in non-adrenergic and non-cholinergic neurons (14). In the esophagus autonomic plexus of these patients, lack of neuronal nitric oxide synthase has been shown (15). In this syndrome, achalasia typically occurs before age 16, and it is diagnosed with adrenal failure either synchronically or 1-4 years before the development of adrenal failure (13). In our case, the diagnosis of achalasia had not been made before age 16 as it was identified in literature, however, adrenal insufficiency had developed 3 years after the diagnosis of achalasia. Triple A syndrome presenting with achalasia in adults is rare in the literature (15). Neurological findings constitute another component of the syndrome. Progressive neurological impairment is seen with age in 60% of patients (11,16). Endocrinological and gastrointestinal symptoms are predominantly observed, and the majority of the cases are seen to first manifest these symptoms (16,17). The majority of patients diagnosed at a late stage predominantly present with neurological symptoms (17,18,19,20). The most remarkable neurological findings are reduced lacrimation, pupillary abnormalities, orthostatic hypotension, sexual impotence, palpitation and abnormal intradermal histamine reaction, all of which can be considered to be findings of autonomic dysregulation (21,22). In our case, alacrima and orthostatic hypotension, which are among the findings of autonomic dysregulation, existed; no parasympathetic autonomic disorder was detected by autonomic testing. In this syndrome bulbar involvement, peripheral and pyramidal sings can also be frequently observed (4,18,22). Electromyography showed pes cavus in both feet, slowed ulnar, median, peroneal, and posterior tibial motor nerve conduction rates and lowered compound tissue nerve conduction rates. Sensory conduction velocities were normal. The findings were compatible with distal symmetrical peripheral neuropathy. The mechanism of neurological findings in triple A syndrome is not clear. The increased sensitivity may be a major mechanism for the neurodegeneration (23).

Conclusion

Most patients diagnosed with triple A syndrome at a late stage predominantly present with neurological symptoms. Whereas,

adrenal failure may rarely occur in advance age. Adrenal failure is the most important determinant in the prognosis of the disease in terms of its diagnosis and treatment. Thus, it would be much more tempting to say that patients diagnosed with achalasia and alacrima as well as with neurological findings should also be considered for adrenal failure and followed up accordingly.

Conflicts of Interest

There are no conflicts of interest.

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