Alacrima-Achalasia: Look for Adrenal Insufficiency: Case Report

Alakrima-Akalazya: Adrenal Yetmezlik Açısından İzlem

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ABSTRACT Triple A syndrome is a rare autosomal recessive disorder characterized by alacrima, adrenocorticotropic hormone resistant adrenal insufficiency and achalasia. The clinical findings can be heterogeneous. Neurological findings such as autonomic dysfunction may accompany this syndrome, and therefore, it is sometimes called as 4 A syndrome. This report describes a 7-year-old girl presented with a hypoglycemic seizure to emergency. She had tonsillitis, dark cutaneous pigmentation and unnoticed alacrima. It was learned that she was operated for achalasia at the age of 5 years. The clinical and laboratory findings were consistent with adrenal insufficiency and she was diagnosed as Triple A syndrome. As the components of Triple A syndrome may develop at different times, careful follow-up should be done in patients with achalasia and alacrima in respect of adrenal insufficiency.

Key Words: Adrenal insufficiency; Achalasia Addisonianism Alacrimia syndrome; autonomic nervous system

ÖZET Triple A sendromu alakrima, adrenokortikotropik hormon dirençli adrenal yetmezlik, akalazya ile karakterize, nadir görülen otozomal resesif geçişli bir hastalıktır. Klinik bulgular heterojendir. Otonom sinir sistemi disfonksiyonu gibi nörolojik bulgular bu sendroma eşlik edebilir. Bu nedenle 4 A sendromu da denilmektedir. Bu makalede, 7 yaşında hipoglisemiye bağlı nöbet ile acil servise başvuran bir kız hasta sunulmuştur. Muayenesinde tonsilit, cilt renginde koyulaşma ve daha önceden fark edilmemiş olan gözyaşı yokluğu tespit edilmiştir. Hastanın 5 yaşındayken akalazya nedeniyle ameliyat olduğu öğrenilmiştir. Klinik ve laboratuvar bulguları adrenal yetmezlik ile uyumlu bulunan hastaya Triple A sendromu tanısı konulmuştur. Triple A sendromunun bileşenleri farklı zamanlarda gelişebileceği için, akalazya ve alakriması olan hastalar adrenal yetmezlik açısından yakın izlenmelidir.

Anahtar Kelimeler: Adrenal yetmezlik; Akalazya Addisonianizm Alakrima sendromu; otonom sinir sistemi

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Triple A syndrome or Allgrove syndrome (OMIM# 231550) is a rare autosomal recessive disorder characterized by adrenocorticotropic hormone (ACTH) resistant adrenal failure, achalasia and alacrima.[1] Autonomic dysfunction, neurological and dermatological features may accompany this syndrome, and therefore, it is sometimes called as 4 A syndrome.[2]

Sometimes, whole component of this syndrome can not be detected on admission, and patients can be followed up with only achalasia or alacrima.

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Especially adrenal insufficiency as a life-threatening component of Allgrove syndrome can be overlooked. Here, we present a 7-year-old patient who had operated for achalasia three years before the diagnosis of adrenal insufficiency. The parents gave written and informed consent.

CASE REPORT

A 7-year-old female was admitted to the pediatric emergency department with the complaints of fever, sore throat, vomiting, and seizure. Physical examination revealed a blood pressure of 100/76 mmHg, pulse of 108 bpm, and body temperature 38 ^{0}C. Her body measurements were weight 18 kg (3-10p), height 114 cm (3-10p), height standard deviation score -1.53, body mass index 14 kg/m^2 and relative body mass index 88%. She had nasal speech and cryptic tonsillit. Increased pigmentation was observed on her skin over joints, incision scar, tongue and gums (Figure 1 and 2). Cardiovascular, respiratory and neurological examinations were normal. Further investigation revealed that she had applied to emergency department about one month ago with fever, vomiting and diarrhea and been followed up with hyponatremic (Na:129 mEq/L) dehydration for 3 days.

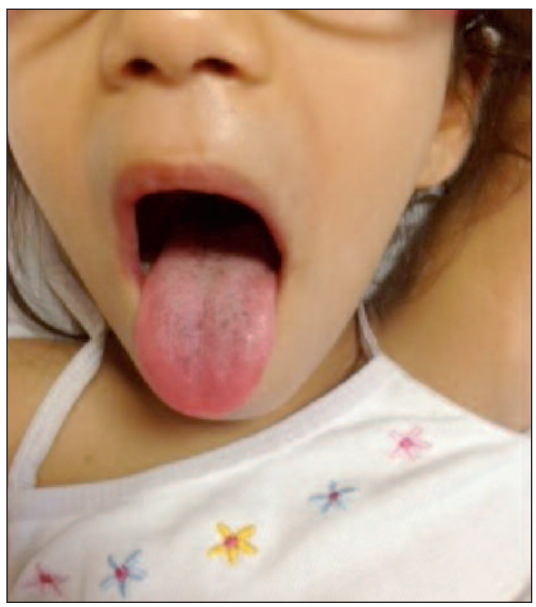

FIGURE 1: Hyperpigmentation on tongue of the patient.

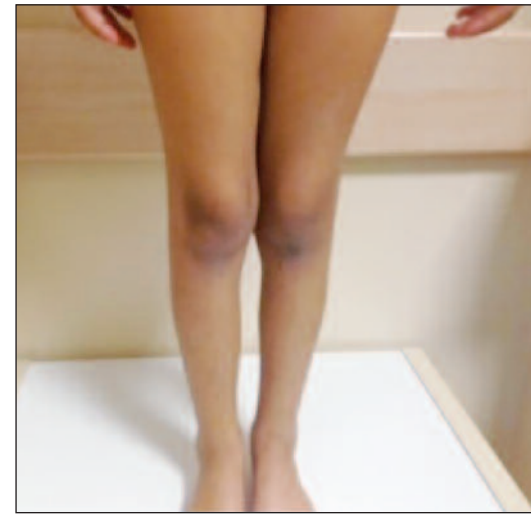

FIGURE 2: Hyperpigmentation on extremities of the patient.

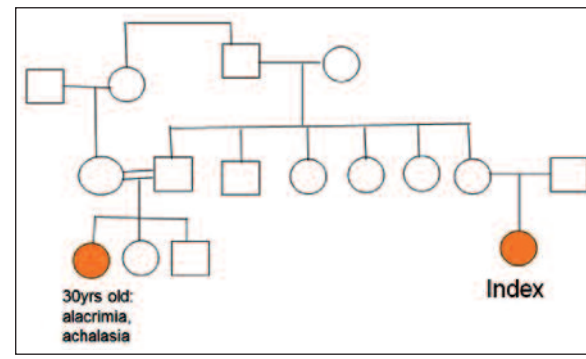

FIGURE 3: The pedigree of the patient's family.

The patient had applied to a gastroenterologist with intermittent vomiting since she was one year old. Therapy for gastroesophageal reflux was failed. She had diagnosed with achalasia when she was 4 years old. Cardiomyotomy and Nissen funduplication were performed at 5 years of age. Her mother reported that she cried without tears since infancy. She was the first and only child of non-consanguineous parents. She had a relative who was followed up with achalasia and alacrima (Figure 3).

When she first applied with seizure the blood glucose level was 25 mg/dL, Na:135 mEq/L, K:3,7 mEq/L and Cl:110 mEq/L. The patient, who had resistant hyponatremia previously (Na:129 mEq/L), hypoglycemic seizure and hyperpigmentation was suspected to have adrenal insufficiency. Basal cortisol and ACTH levels were found to be 10,6 µg/mL (normal range: 6,2-19,4) and >2000 pg/mL (normal

range: 7,2-63,3) respectively. ACTH insensitivity was diagnosed and hydrocortisone substitution therapy with 30 mg/m^2/d was started. The dose was adjusted according to serum electrolyte and hormone values to 10 mg/m^2/d. Plasma renin activity (PRA): 34 ng/mL/hr (normal range: 0,48-4,88) and aldosterone: 7,16 mg/dL (normal range: 2,7-27). Hyponatremia, increased PRA with normal serum aldosterone levels pointed to additional mineralocorticoid deficiency. However, after hydration and substitution therapy with 30 mg/m^2/d hydrocortisone, Na: 137 mEq/L and PRA:0,85 ng/mL/hr returned to normal levels. So mineralocorticoid treatment was postponed and the patient has been followed up carefully for a possible mineralocorticoid deficiency.

On the last examination at 8.5 years of age, she was 22.3 kg-116.5 cm and her hyperpigmentation improved. Serum electrolytes and PRA were still within normal ranges.

Eye involvement is a part of triple A syndrome. The examination showed that ocular motility was full and without nystagmus. Clinically, there was no significant anisocoria. There was no afferent pupillary defect and direct and indirect light reflexes were normal. Slit lamp biomicroscopy examination revealed grade 4 severe corneal and conjunctival staining in both eyes. Schirmer test results without anesthesia were 0 mm in both eyes. It is interpreted as dry eye when the wetted part of the Shirmer paper is <5 mm with the eyes closed for 5 minutes. Dilated fundus examination revealed temporal pallor of the optic discs. On magnetic resonance imaging (MRI), patient was found to have severe hypoplasia of both lacrimal glands (Figure 4). Topical cyclosporin ophthalmic emulsion 0.05% and aggressive lubrication with preservative-free artificial tears were prescribed. On follow-up examinations degree of corneal and conjunctiva staining decreased and the patient had partial relief of her symptoms.

The clinical features established triple A syndrome. The patient was examined for neuropathy. The neurological examination was normal. The electromyoneurography (EMNG) demonstrated mild axonal polyneuropathy at the lower extremities (n. medianus 72m/sec, n. suralis 47m/sec)

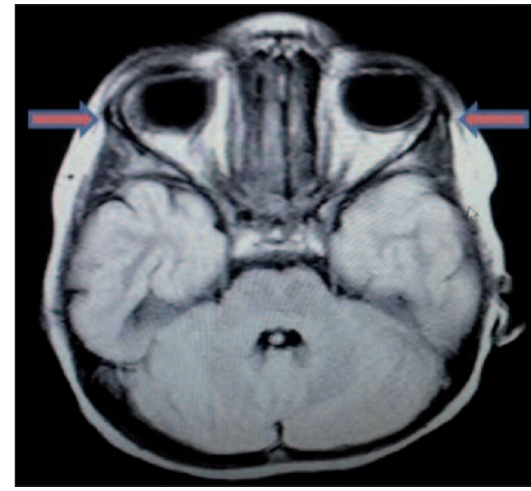

FIGURE 4: Orbital MRI shows bilateral hypoplastic lacrimal glands (red arrows).

She is currently clinically well and being followed up by endocrinology, neurology and ophthalmology departments.

DISCUSSION

The triple A syndrome is a rare autosomal recessive disorder characterized by adrenal failure, achalasia and alacrima.[1] It affects two main systems in the body: the nervous system and the adrenal cortex. Our patient had alacrima and achalasia but these findings were not noticed as part of a syndrome until she applied to emergency with hypoglycemic crisis.

She developed swallowing difficulties and vomiting when she was 3; and a surgery was performed for achalasia at 5 years of age. Like in our patient; achalasia of the cardia, usually begins at early childhood, occurs in 75% of patients and is the first sign that leads parents to seek for medical advice.[3,4]

Alacrima or hypolacrima is usually the earliest and most consistent sign of this syndrome. Tearing, normally, in response to crying may take several months after birth. Alacrima is very uncommon condition in children. It is easy to overlook the inherited lacrimal diseases.These disorders may have associated conditions and recognition of the lacrimal abnormalities may be central in establishing the correct diagnosis. It may result from the absence or hypoplasia of the lacrimal gland or ab-

normalities of the nervous system controlling the lacrimation. There are two disorders associated with alacrima due to autonomic dysfunction: the triple A disease and Riley-Day syndrome. Riley-Day syndrome, also known as familial dysautonomia, is an autosomal recessive disorder with systemic manifestations of blood pressure lability, blotchy skin when agitated and a generalized reduction in sensitivity to pain.[5,6] In our patient, glucocorticoid deficiency accompanying alacrima is consistent with triple A syndrome. The clinical findings of Riley-Day syndrome such as blotchy skin and reduction in sensitivity to pain were missing in the patient.

ACTH insensitivity syndromes are a group of rare hereditary disorders. There are two main disorders result in unresponsiveness to ACTH: Triple A syndrome and Familial Glucocorticoid Deficiency (FGD). They are due to the inability of ACTH to stimulate steroidogenesis in the adrenal cortex. FGD is a rare autosomal recessive disorder that is characterized by severe cortisol deficiency, high plasma ACTH levels and typically, a well-preserved renin-angiotensin-aldosterone axis. It usually presents at neonatal and early childhood. Recurrent infections, failure to thrive, coma and neonatal hepatitis can be a part of the disease.[7] Triple A syndrome is distinguished from FGD with characteristic clinical findings such as alacrima and achalasia. The family history of FGD was absent in our patient. In triple A syndrome, isolated glucocorticoid deficiency is seen in approximately 80% of patients with additional mineralocorticoid deficiency observed in 15%.[8] Additional mineralocorticoid deficiency suspected for our patient at the first presentation. However, after hydration and hydrocortisone substitution therapy, serum Na, K, PRA and aldosterone levels were within the normal ranges. The patient has been followed up for a possible future mineralocorticoid deficiency.

Triple A syndrome is a heterogeneous disorder that the presentation can be variable. Neurologic features of this syndrome are motor, sensory and autonomic impairment. Autonomic dysfunction includes alacrima, achalasia, orthostatic hypotension, arrhytmia, abnormal intradermal histamine reaction. Neurologic symptoms are present usually in patients diagnosed at a late stage. The other neurologic findings are cranial nerve weakness resulting in dysarthria and nasal speech, distal limb muscle wasting and weaknesss, hyperreflexia, ataxia, optic atrophy, sensorineural deafness, mental retardation and rarely sensory impairment.[2,9,10] Nerve conduction studies usually reveal an axonal motor neuropathy. After the patient was diagnosed with triple A syndrome, the common neurologic findings were examined. Although our patient had a normal neurological exam, the only finding was mild distal axonal polyneuropathy on EMNG.

This syndrome is caused by homozygous or compound heterozygous mutations in the *AAAS* (Achalasia-Addisonism-Alacrima syndrome) on chromosome 12q13.13 encoding the nuclear pore complex protein ALADIN. ALADIN mutations lead to impaired nuclear import and it was shown that this results in susceptibility to cellular oxidative stress. The adrenal failure and autonomic dysfunction are the most important determinants of prognosis.[3,11] The eventual determination of the exact functional roles of ALADIN will provide insight in the pathogenesis of the triple A syndrome and may suggest future therapies.

As a conclusion, most of the patients with triple A syndrome can be overlooked until they apply with hypoglycemic crisis. Not all patients have the whole main features characterizing this syndrome. The components of triple A syndrome may develop at different times and can be subtle requiring further investigation for diagnosis. Careful follow up should be done in aspects of adrenal insufficiency in patients with achalasia and alacrima.

REFERENCES

1. Allgrove J, Clayden GS, Grant DB, Macaulay JC. Familial glucocorticoid deficiency with achalasia of the cardia and deficient tear production. Lancet 1978;1(8077):1284-6.
2. Kimber J, McLean BN, Prevett M, Hammans SR. Allgrove or 4 "A" syndrome: an autosomal recessive syndrome causing multisystem neurologic disease. J Neurol Neurosurg Psychiatry 2003;74(5):654-7.
3. Dumic M, Barišic N, Kusec V, Stingl K, Skegro M, Stanimirovic A, et al. Long-term clinical follow-up and molecular genetic findings in eight patients with triple. A syndrome. Eur J Pediatr 2012;171(10):1453-9.
4. Philip M, Hershkovitz E, Schulman H. Adrenal insufficiency after achalasia in the triple A syndrome. Clin Pediatr (Phila) 1996;35(2):99-100.
5. Moore BD. Lacrimal system abnormalities. Optometry & Vision Science 1994;71(3):182-3.
6. Allen RC. Hereditary disorders affecting the lacrimal system. Curr Opin Ohtalmol 2014; 25(5):424-31.
7. Lacy DE, Nathavitharana KA, Tarlow MJ. Neonatal hepatitis and congenital insensitivity to adrenocorticotropin (ACTH). J Pediatr Gastroenterol Nutr 1993;17(4):438-40.
8. Cooray SN, Chan L, Metherall L, Storr H, Clark AJ. Adrenocorticotropin resistance syndromes. Endocr Dev 2008;13:99-117.
9. Dixit A, Chow G, Sarkar A. Neurologic presentation of triple a syndrome. Pediatr Neurol 2011;45(5):347-9.
10. Makari G, Hoffman WH, Carroll JE, Savage DR, Van der Zalm T. Autonomic dysfunction and adrenocortical unresponsiveness to ACTH. J Child Neurol 1988;3(3):174-6.
11. Hirano M, Furiya Y, Asai H, Yasui A, Ueno S. ALADIN1482S causes selective failure of nuclear protein import and hypersensitivity to oxidative stress in triple A syndrome. Proc Natl Acad Sci USA 2006;103(7):2298-303.