



Two Siblings with Triple-A Syndrome: Endocrinologic and Neurologic Features

Triple A Sendromlu İki Kardeş: Endokrinolojik ve Nörolojik Özellikler

• Nilüfer Özdemir Kutbay, • Fatma Keklik*, • Banu Sarer Yürekli, • Gökçe Kavasoglu**, • Nevin Oruç***, • Mehmet Erdoğan, • Şevki Çetinkalp, • Gökhan Özgen, • Füsün Saygılı

Ege University Faculty of Medicine, Department of Endocrinology and Metabolism, İzmir, Turkey

*Ege University Faculty of Medicine, Department of Internal Medicine, İzmir, Turkey

**Ege University Faculty of Medicine, Department of Neurology, İzmir, Turkey

***Ege University Faculty of Medicine, Department of Gastroenterology, İzmir, Turkey

Abstract

Triple-A syndrome is a rare, multi-systemic disease and is characterized by adrenal insufficiency, achalasia, or alacrima. The symptoms may also involve neurologic manifestations, including pyramidal findings and peripheral motor neuropathy. Other findings include autonomic dysfunction and cerebellar ataxia. In the present study, we present the case of two siblings with triple-A syndrome with neurologic manifestations. The neurologic abnormalities can lead to misdiagnosis owing to resemblance to the manifestations of other neurologic disorders. Therefore, the cases with triple-A syndrome should be carefully evaluated and examined for clinical and neurophysiologic signs.

Keywords: Triple-A syndrome; adrenal insufficiency; peripheral neuropathy

Özet

Triple A Sendromu nadir bir multisistemik hastalıktır ve adrenal yetmezlik, alakrima veya akalazyaya ile karakterizedir. Semptomlar, piramidal bulgular ve periferik motor nöropati de dahil olmak üzere nörolojik belirtileri de içerebilir. Diğer bulgular arasında otonomik disfonksiyon ve serebellar ataksi bulunur. Bu çalışmada, nörolojik bulguların eşlik ettiği Triple A Sendromlu iki kardeşi sunuyoruz. Bu nörolojik anormallikler diğer nörolojik hastalıkların bulgularına benzerliği nedeniyle yanlış tanıya yol açabilir. Bu nedenle, Triple-A sendromu olan olgular dikkatlice değerlendirilmeli, klinik ve nörofizyolojik olarak incelenmelidir.

Anahtar kelimeler: Triple-A sendromu; adrenal yetmezlik; periferik nöropati

Introduction

Triple-A syndrome is an autosomal recessive disorder that was first described in 1978 by J. Allgrove (1). Most prominent characteristics of triple-A syndrome include esophageal achalasia, alacrima, and adrenal insufficiency. It is a rare and multi-systemic syndrome, characterized by progressive nerve degeneration; autonomic nerve system findings could also be present (2). It is a genetic disorder with an autosomal recessive pattern involving a mutation in the AAAS (Achalasia-Addisonianism-Alacrima Syndrome) gene coding for the protein called ALADIN (Achalasia Achalasia aDrenal Insufficiency Neu-

rologic disorder) (3,4). The neurologic manifestations of the syndrome have largely been ignored and not extensively studied for a long time. Gazzarian et al. defined this syndrome as 4A instead of 3A owing to the association with autonomic nervous system findings (5). In the present study, we present two cases with the diagnosis of triple-A syndrome where we studied the association of this syndrome with neurologic manifestations.

Case 1

A 28-year-old female patient presented with hyperpotassemia, hyperpigmentation, and hypocortisolemia and was initially diagnosed with adrenal

Address for Correspondence: Nilüfer Özdemir Kutbay, Ege University Faculty of Medicine, Department of Endocrinology and Metabolism, İzmir, Turkey

Phone: 0412 258 00 60 **E-mail:** nozdemirkutbay@hotmail.com **Received:** 25/02/2016 **Accepted:** 08/09/2016

©Copyright 2018 by Turkish Journal of Endocrinology and Metabolism Association
Turkish Journal of Endocrinology and Metabolism published by Türkiye Klinikleri

insufficiency. She was referred to our hospital with complaints of weakness and fatigue at the age of 11 years. She was later referred to the gastroenterology department with complaints of dysphagia when she was 18 years old and on hydrocortisone treatment. Esophagography revealed achalasia and balloon dilatation was performed (Figure 1a, 1b). After the detection of xerophthalmia, she was diagnosed with triple-A syndrome due to the presence of alacrima with adrenal insufficiency and achalasia. As her weakness and fatigue persisted, she was examined for neurologic signs. Deep tendon reflexes were increased with the presence of proximal muscle weakness. The findings of electromyography (EMG) were compatible with axonal sensory-motor polyneuropathy (Table 1). Autonomic neuropathy tests were normal.

Case 2

A 21-year-old male patient (brother of Case 1) was examined at the age of three years owing to family history and diagnosed with adrenal insufficiency and achalasia. He was referred to our clinic with the development of xerophthalmia and was diagnosed with triple-A syndrome. We conducted balloon dilatation to treat achalasia in the gastroenterology department. His blood pressure was 100/60 mmHg, and he complained of weakness and fatigue. His 25-hydroxylase vitamin D level was 35 nmol/L and was administered the initial loading dose of vitamin D replacement. Later, the maintenance dose was preferred. Neurologic examination revealed increased deep tendon reflexes and dysarthria. Muscles were atrophic in all extremities (Figure 2a, 2b). EMG findings suggested polyneuropathy. However, motor neuropathy was the dominant manifesta-

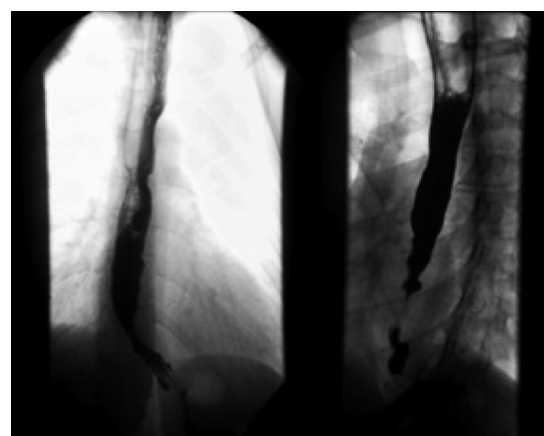


Figure 1: a) Esophageal constriction b) Scene of esophagus after dilatation (Case 1).

tion in EMG (Table 2). Autonomic neuropathy tests were normal.

Discussion

The patients with triple-A syndrome usually present endocrinologic and gastroenterologic symptoms at the time of diagnosis. Neurologic manifestations could be seen later, leading to these getting missed out if the clinician is unaware of the presence of neurologic manifestations. Here, we present two cases with triple-A syndrome with neurologic manifestations.

Triple-A syndrome is primarily characterized by adrenal insufficiency, achalasia, and alacrima. Adrenal insufficiency and achalasia are usually manifested during the first decade of life. Achalasia is present in about 75% of cases and usually manifests as dysphagia, especially for liquids, whereas adrenal insufficiency manifests as hypoglycemia and hypotension. Main features of ad-

Table 1. Neuropsychologic examination of case 1.

	Amplitude (CMAP:mV, SNAP: μ V)		Distal latency (msec)		Conduction Velocity (m/sec)	
	R	L	R	L	R	L
Median SNAP	21 (>20)	24 (>20)	2.1 (>3.8)	2 (>3.8)	59 (>45)	55 (>45)
Ulnar SNAP	12 (>20)	15 (>20)	2.4 (>3.8)	2.2 (>3.8)	49 (>45)	57 (>45)
Median CMAP	10 (>5)	7 (>5)	3 (>3.9)	3.1 (>3.9)	55 (>50)	52 (>50)
Ulnar CMAP	2 (>5)	0.5 (>5)	4.5 (>3.1)	3.4 (>3.1)	43 (>50)	49 (>50)
Peroneal CMAP	3.5 (>4)		3.8 (>4.7)		45 (>40)	
Posterior tibial CMAP	1 (>5)		4.7 (>5.5)		45 (>40)	
Sural SNAP	NR (>8)	NR (>8)				

CMAP: Compound Muscle Action Potential; SNAP: Sensory Nerve Action Potential; NR: No response.



Figure 2: a) Hand muscle atrophy (Case 2) b) Pes cavus (Case 2).

renal insufficiency include fatigue, loss of appetite, weight loss, low blood pressure, and darkening of the skin. It occurs due to primary adrenal insufficiency. Mineralocorticoid production is preserved in most patients with triple-A syndrome but may be impaired in 15% of patients. The third major feature of triple-A syndrome is a reduced or absent ability to secrete tears (alacrima). Most people with triple-A syndrome have all three features, although some present only two (6).

The retrospective study conducted by Vallet et al. (7) presented eight cases of triple-A syndrome with neurologic manifestations. Age at the onset ranged from one month to 20 years. Two cases manifested symptoms during early childhood and included adrenal insufficiency and achalasia. Neurologic symptoms in these cases were noticed during teenage. The other six cases presented neurologic symptoms as initial symptoms that occurred from early childhood to early adulthood. There was a delay of at least 17 years before the diagnosis of triple-A syndrome was made. When

adrenal insufficiency and achalasia are present at the time of diagnosis of triple-A syndrome, neurologic dysfunction could be coexisting. In pediatric cases of triple-A syndrome, adrenal insufficiency, achalasia, and alacrima are usually present at the time of diagnosis; however, these could be missing in adult- or late-onset triple-A syndrome. Thus, in patients presenting neurologic dysfunction as the predominant clinical manifestation, it is useful to search for the history of achalasia and alacrima and perform hormone assay for adrenal insufficiency. The main neurologic pathology, in eight cases reported by Vallet et al. (7), included pyramidal syndrome and peripheral neuropathy. Peripheral neuropathy resulted in distal wasting and orthopedic deformation such as pes cavus (7). Further, motor fibers were more affected, and few patients had a sensory deficit. In the present study, the cases manifested sensory-motor neuropathy. The EMG findings of the two cases are presented in Table 1 and 2. A decrease in amplitude values was compatible with axonal neuropathy. EMG values revealed motor neuropathy to be more prominent. Needle EMG also ruled out myopathy. The EMG recordings pointed to sensory-motor neuropathy in our cases that resulted in wasting of hand muscles and pes cavus in case 2. The differential diagnosis of axonal sensorimotor peripheral polyneuropathy revealed a dominant hereditary polyneuropathy due to distinct muscular atrophy in distal muscles. However, this diagnosis was eliminated owing to the absence of similar symptoms in upper zones and the absence of an increase of deep tendon reflexes in the neurologic examination. The laboratory test, done for acquired polyneuropathy, revealed nor-

Table 2. Neurophysiologic examination of case 2.

	Amplitude (CMAP:mV, SNAP: μ V)	Distal latency (msec)	Proximal latency (msec)	Conduction Velocity (m/sec)
	R	R	R	R
Median SNAP	12 (>20)	2.6 (>3.8)		42 (>45)
Ulnar SNAP	17 (>20)	2.4 (>3.8)		47 (>45)
Median CMAP	10 (>5)	4.1 (>3.9)	10.7	38 (>50)
Ulnar CMAP	0.4 (>5)	4.5 (>3.1)	10.2	34 (>50)
Peroneal CMAP	2 (>4)	6.1 (>4.7)	16.1	31 (>40)
Posterior tibial CMAP	0.4 (>5)	5.2 (>5.5)	16.3	34 (>40)
Sural SNAP	10 (>8)	3.7 (>3.8)		38 (>45)

CMAP: Compound Muscle Action Potential; SNAP: Sensory Nerve Action Potential.

mal values, and no medication was reported in patient's history that could lead to polyneuropathy. In the light of all these, neuropathy was considered to be associated with this syndrome along with the presence of usual symptoms of the syndrome.

Autonomic neuropathy and ataxic gait originating from cerebellum were present in the cases studied by Vallet et al. (7). These were not observed in our cases. Autonomic dysfunction, such as orthostatic hypotension, bladder dysfunction, diarrhea or constipation, sexual dysfunction, and dyshidrosis, was present in six cases reported by Vallet et al. (7). Bulbar and facial deficiencies were observed in all eight patients; velar insufficiency, tongue amyotrophy, and orbicularis oris dysfunction were observed to various degrees (7). In our study, case 2 had dysarthria as a bulbar dysfunction. Bulbar symptoms can be confusing and difficult to differentiate from achalasia. Both bulbar dysfunction and achalasia can cause swallowing difficulties. In bulbar dysfunction, dysphagia is associated with dysfunctioning of IX, X, and XI cranial nerves. On the other hand, achalasia only causes lower dysphagia of esophagus. In our cases, no autonomic dysfunction existed.

The cognitive deficit can be present as neurologic manifestation. For instance, cases studied by Vallet et al. (7) presented with frequent and mild cognitive dysfunction; however, this finding was not present.

The neurologic findings misdiagnosed in all patients at the beginning were juvenile amyotrophic lateral sclerosis (ALS), spinocerebellar ataxia, spinal muscular amyotrophy, mitochondriopathy, adrenoleukodystrophy, multiple sclerosis, and Charcot-Marie-Tooth neuropathy (7). The final diagnosis of the triple-A syndrome with neurologic manifestations in the study by Vallet et al. (7) was made by a team of neurologist, gastroenterologist, and endocrinologist. In these eight cases, genetic analysis was also performed, which, unfortunately, could not be performed in our cases.

Apart from the study of Vallet et al., other reports from the literature describe peripheral neuropathy and pyramidal syndrome as other neurologic manifestations (2, 8–10). The most common neurologic manifestation was lower limb weakness in the study of Nakamura et al. (11) who described six cases. All patients presented upper and lower motor neuron signs. Sensory disturbance and autonomic dysfunction were observed

in 29% and 57%, respectively. This study group indicated hyperreflexia as a remarkable finding of triple-A syndrome that distinguished this disease from other causes of peripheral neuropathy. In the present study, increased deep tendon reflexes reflected pyramidal syndrome.

Peripheral nerve pathology is not a well-known finding of triple-A syndrome with an unclear etiology. The presence of sural nerve biopsy has been described by a few reports. The two cases in the present study presented axonal degeneration and a loss of myelinated and unmyelinated nerve fibers (8, 10). Previous reports have attributed the manifestation of neuropathy to a defect in ACTH receptors present on neurons/glia with secondary demyelination; however, further studies did not support this theory (12).

The study of Nakamura et al. (11) involved adult- or late-onset triple-A syndrome with achalasia where the diagnosis was made after neurologic symptoms appeared. Achalasia is an important manifestation of triple-A syndrome diagnosis. All patients in the study conducted by Nakamura et al. had alacrima. On the contrary, adrenal insufficiency was absent in late-onset triple-A cases in the study. Regular follow-ups of these patients are required to keep a check on the levels of cortisone hormone, the non-compliance to which may lead to the missing out of the crisis.

Conclusion

Peripheral neuropathy is a common neurologic finding in patients with triple-A syndrome. The chances of neurologic manifestations getting misdiagnosed as some other neurologic pathologies remain high. Therefore, an association of neurologic manifestations with triple-A syndrome should be considered during its diagnosis. Achalasia and alacrima serve as important clues for the diagnosis. An awareness of the association of neurologic manifestations with triple-A syndrome allows us to follow incomplete neurologic findings with appropriate tests, leading to a better diagnosis.

Author Contributions

Concept: Nilufer Ozdemir Kutbay, Banu Sarer Yurekli, Fatma Keklik, Design: Nilufer Ozdemir Kutbay, Banu Sarer Yurekli, Data Collection or Processing: Nilufer Ozdemir Kutbay, Fatma Keklik, Gokce Kavasoglu, Nevin Oruc, Analysis or Interpretation: Nilufer Ozdemir Kutbay, Banu Sarer Yurekli, Gokce Kavasoglu, Mehmet Erdogan, Literature Search: Nilufer Ozdemir Kutbay, Sevki

Cetinkalp, Gokhan Ozgen, Fusun Saygili, Writing: Nilufer Ozdemir Kutbay, Banu Sarer Yurekli, Fatma Keklik.

Conflict of Interest: No conflict of interest is declared by the authors.

Financial Disclosure: The authors declared that this study received no financial support.

References

1. Allgrove J, Clayden GS, Grant DB, Macaulay JC. Familial glucocorticoid deficiency with achalasia of the cardia and deficient tear production. *Lancet*. 1978;17:1284-1286.
2. Grant D, Barnes N, Dumic M, Ginalska-Malinowska M, Milla PJ, von Petrykowski W, Rowlatt RJ, Steendijk R, Wales JH, Werder E. Neurological and adrenal dysfunction in the adrenal insufficiency/achalasia/achalasia (3A) syndrome. *Arch Dis Child*. 1993;68:779-782.
3. Handschug K, Sperling S, Yoon SJ, Hennig S, Clark AJ, Huebner A. Triple A syndrome is caused by mutations in AAAS, a new WD-repeat protein gene. *Hum Mol Genet*. 2001;10:283-290.
4. Cronshaw JM, Matunis MJ. The nuclear pore complex protein ALADIN is mislocalized in triple A syndrome. *Proc Natl Acad Sci U S A*. 2003;100:5823-5827.
5. Gazarian MM, Cowbell CT, Bonney, Grigor WG. The "4A" syndrome: adrenocortical insufficiency associated with achalasia, alacrima, autonomic and neurological features. *Eur J Pediatr*. 1995;154:18-23.
6. Misgar RA, Pala NA, Ramzan M, Wani AI, Bashir MI, Laway BA. Allgrove (Triple A) syndrome: a case report from the Kashmir Valley. *Endocrinol Metab (Seoul)*. 2015;30:604-606.
7. Vallet AE, Verschuere A, Petiot P, Nicolino M, Roman S, Pouget J, Vial C. Neurological features in adult Triple-A (Allgrove) syndrome. *J Neurol*. 2012;259:39-46.
8. Kimber J, McLean BN, Prevett M, Hammans SR. Allgrove or 4 "A" syndrome: an autosomal recessive syndrome causing multisystem neurological disease. *J Neurol Neurosurg Psychiatry*. 2003;74:654-657.
9. Houlden H, Smith S, De Carvalho M, Blake J, Mathias C, Wood NW, Reilly MM. Clinical and genetic characterization of families with triple A (Allgrove) syndrome. *Brain*. 2002;125:2681-2690.
10. Bentes C, Santos-Bento M, de Sá J, de Lurdes Sales Luís M, de Carvalho M. Allgrove syndrome in adulthood. *Muscle Nerve*. 2001;24:292-296.
11. Nakamura K, Yoshida K, Yoshinaga T, Kodaira M, Shimojima Y, Takei Y, Morita H, Kayanuma K, Ikeda S. Adult or late-onset triple A syndrome: case report and literature review. *J Neurol Sci*. 2010;297:85-88.
12. Stuckey BG, Mastaglia FL, Reed WD, Pullan PT. Glucocorticoid insufficiency, achalasia, alacrima with autonomic and motor neuropathy. *Ann Intern Med*. 1987;106:62-64.