European Journal of Pediatrics (2018) 177:363–369
https://doi.org/10.1007/s00431-017-3068-8

ORIGINAL ARTICLE

Clinical and genetic characterisation of a series of patients with triple A syndrome

Erdal Kurnaz[1] · Paolo Duminuco[2] · Zehra Aycan[1] · Şenay Savaş-Erdeve[1] · Nursel Muratoğlu Şahin[1] · Melişah Keskin[1] · Elvan Bayramoğlu[1] · Marco Bonomi[2,3] · Semra Çetinkaya[1]

Received: 28 October 2017 / Revised: 4 December 2017 / Accepted: 6 December 2017 / Published online: 19 December 2017

Abstract

Triple A syndrome (TAS) or Allgrove syndrome (OMIM #231550) is a rare autosomal recessive disorder characterised by adrenocorticotropic hormone-resistant adrenal insufficiency, alacrima, achalasia, and neurological and dermatological abnormalities. Mutations in the *AAAS* gene on chromosome 12q13 encoding the nuclear pore protein ALADIN have been reported in these patients. Between 2006 and 2017, we evaluated six patients with a clinical diagnosis of TAS, based on the presence of at least two symptoms, usually adrenal insufficiency and alacrima. In all cases, genetic analysis revealed homozygous mutations in the *AAAS* gene. One novel mutation was detected: a homozygous 10-bp deletion (c.1264_1273del, p.Q422NfsX126) in exon 14 of the *AAAS* gene that caused a frameshift that introduced an aberrant stop codon after 126 amino acids. This genetic variant is likely to be pathogenic because it caused a significant change in protein structure. A precise genotype–phenotype correlation was impossible to establish.

Conclusions: Based on our experience, we recommend that molecular analysis should be performed in the presence of alacrima and at least one more symptom of TAS. Our cases share many clinical features of TAS and underline the variability in this syndrome, as well as the need for thorough investigation following a multidisciplinary approach.

What is known:
- *Triple A syndrome is characterised by achalasia, alacrima, adrenal insufficiency, neurological impairment, and dermatological abnormalities.*
- *A precise genotype–phenotype correlation has proved impossible to establish.*

What is new:
- *These cases add to a large number of similar case reports with limited novel information.*
- *The newly identified AAAS gene mutation was reported.*

Marco Bonomi and Semra Çetinkaya contributed equally to this work.

Communicated by Peter de Winter

✉ Erdal Kurnaz
erdalkurnaz44@gmail.com

Paolo Duminuco
p.duminuco@auxologico.it

Zehra Aycan
zehraaycan67@hotmail.com

Şenay Savaş-Erdeve
senaysavas@yahoo.com

Nursel Muratoğlu Şahin
nursel_m_sahin@yahoo.com.tr

Melişah Keskin
meliksah.keskin@hotmail.com

Elvan Bayramoğlu
elvanbayramoglu@gmail.com

Marco Bonomi
m.bonomi@auxologico.it

Semra Çetinkaya
semcetinkaya@gmail.com

[1] Department of Pediatric Endocrinology, Dr. Sami Ulus Obstetrics and Gynecology and Pediatrics Training and Research Hospital, Altındağ, 06020 Ankara, Turkey

[2] Division of Endocrine and Metabolic Diseases and Laboratory of Endocrine and Metabolic Research, IRCCS Istituto Auxologico Italiano, Cusano Milano, Milan, Italy

[3] Department of Clinical Sciences and Community Health, University of Milan, Milan, Italy

Keywords Triple A syndrome · ACTH resistance · Adrenal insufficiency · *AAAS* gene

Abbreviations

ACTH	Adrenocorticotropic hormone
ALADIN	Alacrima, Achalasia, Adrenal Insufficiency, Neurological Disorder
DTR	Deep tendon reflexes
NPC	Nuclear pore complex
PRA	Plasma renin activity
WD	Tryptophan–aspartic acid
TAS	Triple A syndrome

Introduction

Triple A syndrome (TAS) or Allgrove syndrome is an autosomal recessive disease (OMIM #231550) characterised by the triad of achalasia, alacrima, and adrenocorticotropic hormone (ACTH)-resistant adrenal insufficiency. The syndrome is associated with neurological and dermatological abnormalities [5, 12, 17]. It was first described by Allgrove et al. in 1978 [1]. The *AAAS* gene, which is responsible for the disease, was located on chromosome 12q13 in 1996 [20]. Although the precise incidence remains unknown, 77 patients with primary adrenal insufficiency registered in the national database of Turkey were screened for genetic allelic variants; only one case was found to harbour an allelic variant in the *AAAS* gene [8]. According to these data, Allgrove syndrome accounts for approximately 1% of all cases of primary adrenal insufficiency.

The gene product is named alacrima–achalasia–adrenal insufficiency neurological disorder (ALADIN) and is a 546-amino-acid protein that is part of the nuclear pore complex (NPC) controlling nucleocytoplasmic transport. It is located at the central cytoplasmic site of the NPC. ALADIN has four characteristic tryptophan-aspartic acid (WD) repeat domains and belongs to the WD repeat protein family. It mediates the assembly of the NPC, the largest multiprotein assembly in the cell, which is functionally involved in processes such as cell division, protein–protein interactions, transmembrane signalling, transcription, and intracellular trafficking [11, 14, 21]. Several allelic variants of the *AAAS* gene, reported in patients with triple A syndrome, have been demonstrated to result in the mislocalisation of ALADIN in the cytoplasm and in impaired nuclear import [18]. The *AAAS* gene is expressed ubiquitously in human tissues [10], which can explain the systems affected and the diversity of the symptoms observed in triple A syndrome.

In this study, we present six patients with clinical diagnoses of TAS who were treated in our hospital from 2006 to 2017. All but one patient came to our attention following an adrenal crisis, which is the main clinical feature that allowed us to come to a diagnosis. The diagnoses were subsequently confirmed in all of the studied probands by a specific genetic analysis of the *AAAS* gene.

Materials and methods

Clinical data were retrospectively collected from the medical records of the patients in the database for the period 2006 to 2017. Genomic DNA from the patients was extracted from peripheral blood using a Tecan Freedom Evo automatic DNA extractor (Tecan Group, Männedorf, Switzerland) and stored at − 20 °C until use. Exons of the *AAAS* gene (GenBank accession number NM_015665) were amplified by PCR with intron-spanning primers (available upon request) and subsequently sequenced by automated nucleotide sequencing with the Big Dye terminator Ready Reaction Kit ver. 3.1 (Applied Biosystems, Carlsbad, CA, USA). All of the sequence reactions were performed using an ABI Prism 3100® (Applied Biosystems). Sequences with DNA variations were confirmed by a separate DNA extraction, PCR amplification, and sequencing reaction.

Table 1 summarises the genetic and clinical features of all cases.

Results

Case no. 1

This girl was the first child of consanguineous parents. She was admitted to the emergency department at the age of 4 years with a fever, vomiting, and seizures. The patient also had weight loss, severe fatigue, and skin hyperpigmentation. She was then referred to an endocrinologist for these findings. Her medical history included a presentation 1 year earlier with similar complaints and she was diagnosed with meningitis at that time. On physical examination, she was 98 cm (− 1 SD) tall, weighed 13 kg (− 1.68 SD), and had diffuse skin hyperpigmentation. Biochemical and hormonal evaluations revealed a low glucose level (36 mg/dL; normal 60–110), normal electrolyte levels (Na 138 mEq/L, normal 135–145; K 4.24 mEq/L, normal 3.1–5.5), an elevated plasma ACTH level (753 pg/mL, normal 0–46), low cortisol level (< 0.20 μg/dL, normal, 4.1–22), and normal aldosterone and plasma renin activity (PRA) levels. Treatment with hydrocortisone 15 mg/m^2/day was started. Schirmer's test confirmed reduced tear production (2 mm after 1 and 5 min) and keratoconjunctivitis

Table 1 Clinical findings and genetic analysis of six patients with triple A syndrome

Case number	1		2*		3		4		5*		6	
Age (years)	a	b	a	b	a	b	a	b	a	b	a	b
	4	15.3	3	8.5	3.75	7	3.7	5	5	5.75	7.5	8.1
Sex	Female		Male		Male		Male		Male		Male	
Complaints on admission	Fever, seizures, vomiting		Fever, seizures, vomiting, diarrhoea		Fever, seizures		Recurrent vomiting		Weakness		Fever, seizures, vomiting, diarrhoea	
Consanguineous parents	Yes		Yes		Yes		Yes		Yes		Yes	
Allelic variant	R312X		R230X		S263P		*Q422NfsX126*		R230X		p.L356VfsX8	
Main clinical manifestations of TAS												
Alacrima/dry eye	+	+	+	+	+	+	+	+	+	+	+	+
Achalasia/swallowing difficulties	−	+	+	+	−	−	+	+	+	+	+	+
Glucocorticoid deficiency	+	+	+	+	+	+	+	+	+	+	+	+
Clinical manifestations of neurological dysfunction												
Hyperreflexia	−	+	−	+	−	+	−	−	−	−	−	−
Muscle weakness/wasting	−	+	−	−	−	−	−	−	+	+	+	+
Dysarthria/nasal speech	−	+	−	+	−	−	+	+	Speech delay		+	+
Ataxia/clumsiness	−	+	−	−	−	−	−	−	−	−	−	−
Polyneuropathy	−	+	−	−	−	−	−	−	−	−	+	+
Epilepsy	−	+	−	−	−	−	−	−	−	−	+	+
Optic atrophy	−	+	−	−	−	−	+	+	−	−	+	+
Clinical manifestations of autonomic impairment												
Postural hypotension	−	+	−	−	−	−	−	−	−	−	−	−
Increased sweating	−	+	−	−	−	−	−	−	−	−	−	−
Other clinical manifestations												
Mental retardation	−	+	−	−	−	−	−	−	n/a		−	−
Osteoporosis	−	+	−	−	−	−	−	−	−	−	−	−

a, age at diagnosis; b, age at last visit; new mutation in italic; n/a, not available

*First cousins

sicca was diagnosed, whereas funduscopy showed no abnormalities. The barium swallow results were normal.

Her signs and symptoms deteriorated over the course of 11 years. She developed progressive mental retardation, focal epileptic disorder in the right parieto-occipital area on electroencephalography (EEG), a speech disorder with impaired articulation (her speech was normal at the age of 4 years), optic atrophy, impaired left cerebellar tests, weakness in the fine motor abilities of the left extremities, increased sweating, orthostatic hypotension, gait without complete ankle dorsiflexion on the left, brisk deep tendon reflexes (DTR) on the left, difficulty lifting off without support, sensorimotor peripheral polyneuropathy, and achalasia.

Genetic analysis A reported [19] homozygous nonsense mutation in Exon 9 in the *AAAS* gene (c.934C > T, p.R312X, nonsense mutation) was found, for which her mother was heterozygous. No genetic information was obtained from her father, who was not available for analysis.

Case no. 2

A 3-year-old boy was the third child of consanguineous parents. He was admitted to our hospital complaining of vomiting, diarrhoea, and seizures that had been present for 1.5 months, accompanied by progressive hyperpigmentation of the skin. On physical examination, he was 101 cm (1.1 SDS) tall and weighed 14 kg (− 0.46 SDS), and there was hyperpigmentation of the skin. The other physical parameters were normal. Biochemical and hormonal evaluation revealed a normal glucose level (110 mg/dL, normal 60–110), normal electrolyte levels (Na 139 mEq/L, normal 135–145; K 4.4 mEq/L, normal 3.1–5.5), elevated plasma ACTH level (> 1250 pg/mL, normal 0–46), low cortisol level (1.77 μg/dL, normal 4.1–22), and normal aldosterone and PRA levels. Treatment with hydrocortisone 15 mg/m^2/day was introduced. Schirmer's test was not performed because the young patient was not cooperative. Keratoconjunctivitis sicca was found, whereas funduscopy showed no abnormalities. The barium swallow results were normal, although the patient had difficulty swallowing solid food. At the 8.5-year follow-up, he also had nasal speech, increased DTR, and fissured fingers and toes.

Genetic analysis The genetic analysis revealed a reported [11] homozygous substitution (c.688C > T; p.R230X) in exon 7 of the *AAAS* gene that was inherited from his two heterozygous consanguineous parents.

Case no. 3

This boy was the second child of consanguineous parents. He was referred at 3.8 years of age with hypoglycaemia and convulsions. The patient had been admitted 2 months earlier with a fever and seizures and was discharged with a diagnosis of meningitis. On physical examination, he was 99 cm (− 1.25 SDS) tall and weighed 16 kg (−0.47 SDS), and there was hyperpigmentation of the skin. The rest of the physical examination was non-contributory. Biochemical and hormonal tests at the time of a hypoglycaemic episode (glucose 46 mg/dL, normal 60–100) showed normal electrolyte levels (Na 135 mEq/L, normal 135–145; K: 4.3 mEq/L, normal 3.1–5.5), elevated plasma ACTH (> 1250 pg/mL, normal 0–46), low cortisol level (< 0.2 μg/dL, normal 4.1–22), and normal aldosterone and PRA levels. Treatment with hydrocortisone 15 mg/m^2/day was started. Schirmer's test was impossible to perform because the patient was uncooperative. Keratoconjunctivitis sicca was also diagnosed and no abnormalities were found on funduscopy. The barium swallow results were normal. He developed new symptoms, such as increased DTR, over the next 3.2 years.

Genetic analysis Genetic analysis revealed the presence of a homozygous substitution (c.787 T > G; p.S263P) in exon 8 of the *AAAS* gene. This genetic variant has been reported [5, 10, 17]. (The parents were not available for analysis.)

Case no. 4

This boy was the second child of consanguineous parents. At the age of 3.7 years, he came to our attention with recurrent vomiting after feeding, optic atrophy, absence of tears, and eye crusting. On physical examination, he was 96.7 cm (− 1.75 SDS) tall and weighed 15.5 kg (− 0.65 SDS); there was hyperpigmentation of the skin and nasal speech. There were no other relevant findings on physical examination. Hormonal and biochemical testing revealed a normal glucose level (80 mg/dL, normal 60–110), normal electrolyte levels (Na 139 mEq/L, normal 135–145; K 4.7 mEq/L, normal 3.1–5.5), elevated plasma ACTH (> 1250 pg/mL, normal 0–46), low-normal cortisol level (4.64 μg/dL, normal 4.1–22), and normal aldosterone and PRA levels. Treatment with hydrocortisone 20 mg/m^2/day was started. The patient would not cooperate with Schirmer's test. Keratoconjunctivitis sicca was diagnosed, whereas funduscopy was normal. Oesophagography demonstrated achalasia. No new clinical manifestations had developed by the 1.5-year follow-up.

Genetic analysis The analysis revealed a homozygous deletion of 10 bp (c.1264_1273del, p.Q422NfsX126) in exon 14 of the *AAAS* gene that caused a frameshift that introduced an aberrant stop codon after 126 amino acids. The allelic variant was inherited from his two heterozygous unaffected parents.

Case no. 5

A 5-year-old boy was the fourth child of consanguineous parents. He was referred to an endocrinologist because of the results of thyroid function tests: TSH 6.427 μIU/mL (normal 0.6–6.3) and free T4 0.85 ng/dL (normal 0.9–2.1). He had a 2-year history of weakness, fatigue, and lack of appetite. The patient's cousin was being followed at our clinic for Triple A syndrome (Case 2). When the patient's parents were asked about the signs and symptoms of Triple A, they reported that he had not produced tears since birth and they had used artificial tears for the past year; additionally, he had not started speaking yet. On physical examination, he was 109.5 cm (− 0.2 SDS) tall and weighed 17 kg (− 0.71 SDS), and gait disturbance and mild hyperpigmentation of the lips and gingiva were evident, but no other anomalies on physical examination. Hormonal and biochemical investigation revealed a normal glucose level (85 mg/dL, normal 60–110), normal electrolyte levels (Na 139 mEq/L, normal 135–145; K 4.5 mEq/L, normal 3.1–5.5), elevated plasma ACTH (1032 pg/mL, normal 0–45), low cortisol level (< 0.5 μg/dL, normal 4.1–22), and normal aldosterone and PRA levels. Treatment with hydrocortisone 20 mg/m^2/day was started. Schirmer's test could not be performed. Keratoconjunctivitis sicca was found, whereas funduscopy showed no abnormalities. A barium swallow was normal, although the patient had difficulty swallowing solid food. In the following year, he developed fissured fingers and toes.

Genetic analysis The analysis revealed a reported [11] homozygous substitution (c.688C > T; p.R230X) in exon 7 of the *AAAS* gene. Both parents were heterozygous for the same allelic variant.

Case no. 6

A 7.5-year-old boy was referred to our hospital because of cardiopulmonary arrest. He was the first child of consanguineous parents. He had been revived after 5 min of cardiopulmonary resuscitation. On physical examination, he was 124 cm tall (− 0.04 SDS) and weighed 23 kg (− 0.2 SDS); there was hyperpigmentation of the skin and his Glasgow coma score was 3 T. Hormonal and biochemical testing revealed a low glucose level (37 mg/dL, normal 60–110), normal electrolyte levels (Na 135 mEq/L, normal 135–145; K 3.3 mEq/L, normal 3.1–5.5), elevated plasma ACTH (> 1250 pg/mL, normal 0–46), normal cortisol level (12.1 μg/dL, normal 4.1–22), and normal aldosterone and PRA levels. Treatment with hydrocortisone 100 mg/m^2/day was started. After extubation, the dose of hydrocortisone was reduced to 15 mg/m^2/day. Schirmer's test confirmed decreased tear production (2/2 mm), and bilateral optic atrophy was found. A barium swallow was normal. However, the patient had difficulty swallowing solid food. Right frontotemporal epileptic activity was detected on EEG after recurrent seizures and antiepileptic treatment was initiated. Electromyography (EMG) revealed distal symmetric sensorimotor peripheral polyneuropathy. Magnetic resonance imaging of the brain revealed a high-intensity cortical signal and the fluid-attenuated inversion recovery images were consistent with cortical laminar necrosis, with no signs of haemorrhage; this was probably due to the cardiopulmonary resuscitation. At the 6-month follow-up, there were no new manifestations, except for recurrent seizures.

Genetic analysis The analysis revealed a reported [2, 11] homozygous substitution (c.1066_1067del CT; p.L356VfsX8) in exon 11 of the *AAAS* gene. Both parents were heterozygous for the same allelic variant.

Discussion

This study presents the clinical and genetic characteristics of six patients (five boys, one girl) who were diagnosed with TAS in our department. TAS is a rare cause of primary adrenal insufficiency. All patients were the children of consanguineous unaffected parents and the final diagnosis was reached before 5 years of age in all but one case.

Four cases were diagnosed after hypoglycaemic episodes associated with an unmet relative increase in glucocorticoid requirements due to infection; one case was diagnosed during a workup for vomiting and eye crusting; and one case was diagnosed during an investigation of elevated TSH levels that were detected in an investigation of weakness. The signs of adrenal insufficiency were mistakenly interpreted as an infection in cases 1 to 3 and 6, and these patients initially underwent incongruous investigations and received inappropriate therapies. Indeed, a delayed diagnosis is likely, particularly when the patients do not come to the attention of a paediatric endocrinologist, who is usually more aware of the clinical presentation of TAS.

At the time of diagnosis, all six of our cases had adrenal insufficiency and alacrima, while four also had achalasia, and three had neurological disorders. During follow-up, five patients developed difficulty swallowing or achalasia, as demonstrated on oesophagography, and all cases had severe or mild neurological disorders.

The adrenal insufficiency in TAS usually manifests during the first decade of life. In our group, five cases had both clinical and laboratory signs of adrenal insufficiency and needed replacement therapy at the time of diagnosis. In accordance with the literature [3, 5, 12], the adrenal insufficiency in our cases manifested as episodic attacks of hypoglycaemia and progressive hyperpigmentation. Although alacrima was often the earliest sign of disease, all patients but one were diagnosed

based on the symptoms of adrenal insufficiency, as in earlier studies [1, 3, 5, 12, 17]. The mechanism of the adrenal insufficiency in patients with TAS is thought to be the result of ALADIN protein dysfunction. Failure of ALADIN function plays a role in redox homeostasis in human adrenal cells and inhibits steroidogenesis [16]. In our patients, the normal electrolyte levels indicated normal mineralocorticoid production and aldosterone levels. Although most patients with TAS have preserved mineralocorticoid production, it may be impaired in some cases [7, 13].

Alacrima is an early symptom of TAS, and may appear during early infancy [1, 3, 5, 7, 12, 13, 16, 17]. Similarly, the initial manifestation of TAS in our cases was decreased tear production. If the alacrima had been considered earlier, perhaps the emergency adrenal crisis could have been avoided in cases no. 1 to 3 and 6. Alacrima has been overlooked in many of the reported cases of TAS because alacrima does not always prompt parents to seek professional help for their children, unless they have eye discomfort [1, 3, 5, 12, 17]. The decreased tear production probably results from dysfunction of the parasympathetic nervous system. If tear production is deficient, physicians should inquire about the clinical features associated with TAS to avoid a potentially fatal adrenal crisis.

Typically, achalasia in TAS presents with vomiting, swallowing difficulties, weight loss, and a chronic cough [3, 9]. These symptoms may occur for years before a diagnosis of achalasia is made [3, 5, 7, 9, 12, 13, 15, 16]. In cases no. 1, 2, and 4 to 6, these symptoms were present at diagnosis. Achalasia was present in one patient at the time of diagnosis (no. 4), whereas the remaining patients had swallowing difficulties, except for case no. 3. The symptoms are usually progressive [5, 9, 12]. In our first patient, a barium swallow 9 years after the diagnosis demonstrated achalasia.

Neurological dysfunction due to involvement of the central, peripheral, or autonomic nervous systems is often associated with TAS. The triad of achalasia, alacrima, and ACTH-resistant adrenal insufficiency are usually evident by the end of first decade, and neurological symptoms such as hyperreflexia, dysarthria, hypernasal speech, ataxia, sensory impairment, muscle weakness, developmental delay, and mental retardation can manifest after this [1, 3, 5–7, 12, 13, 16, 17]. Similar to the reported cases, our first case slowly developed ataxia, polyneuropathy, epilepsy, optic atrophy, and progressive mental retardation. Cases 2 and 4 developed mild neurological impairment in the first decade. Hyperreflexia (no. 1 to 3), nasal speech (no. 1, 2, 4, and 6), and muscle weakness/wasting (no. 1, 5, and 6) were seen in our cases. In case no. 5, the speech delay was thought to be due to delayed neurological development. Other neurological manifestations, such as optic atrophy can develop over time [5, 12], as in our cases 1, 4, and 6. Autonomic neuropathy is also frequently associated with TAS [5, 12], and case 1 manifested clinical features of autonomic dysfunction, such as postural hypotension and increased sweating. Nevertheless, these neurological findings can be misdiagnosed when the diagnosis of TAS is not considered. In such cases, the clinician might also consider adrenoleukodystrophy and Charcot–Marie–Tooth disease [4, 5, 12]. Our cases demonstrate the usefulness of screening for mutations in the *AAAS* gene when neurological impairment is associated with at least one other typical feature of TAS.

Mutations in the *AAAS* gene include missense, nonsense, frameshift, and splice-site mutations and can be homozygous or compound heterozygous in pedigrees with the disease. All of our cases had homozygous allelic variants, according to the autosomal recessive inheritance of TAS: four nonsense variants (67%) and two base-pair deletions (33%) in the *AAAS* gene (Table 1). The allelic variants were inherited from consanguineous parents who had no typical symptom or signs of TAS. We did not find any genotype–phenotype correlations when we compared our cases with reported mutations [2, 5, 10, 11, 17, 19]. A genetic analysis of the case 4 variant has not been reported, although it is likely to be pathogenic because of the major change in protein structure.

In conclusion, the wide spectrum of the clinical presentation of TAS reflects the pleiotropic function of the ALADIN protein. No genotype–phenotype correlations have been reported [5, 11, 12, 14, 17], or were noted in our patient series. Although TAS is rare, it should be considered in every child with alacrima. Based on our experience, we recommend adrenal function testing and molecular analysis in the presence of alacrima and at least one more symptom of TAS. Indeed, an early diagnosis of TAS is crucial as it prevents unnecessary investigations and inappropriate treatment.

Authors' contributions Study concept and design: EK, PD, ZA, MB, and SC. Acquisition of data: EK, ZA, SSE, NMS, MK, EB, MB, and SC. Analysis and interpretation of data: EK, PD, and MB. Drafting the manuscript: EK and MB. Critical revision of the manuscript for important intellectual content: EK, MB, and SC. Final approval of the version to be published: all authors.

Compliance with ethical standards

Ethical approval The study was conducted in accordance with the principles of the Declaration of Helsinki and was approved by the Local Ethics Committee.

Informed consent Blood samples from patients and family members were collected for genetic testing after obtaining written informed consent.

Conflict of interest The authors declare that they have no conflict of interest.

References

1. Allgrove J, Clayden GS, Grant DB, Macaulay JC (1978) Familial glucocorticoid deficiency with achalasia of the cardia and deficient tear production. Lancet 1(8077):1284–1286
2. Appak YÇ, Çam FS, Evirgen Şahin G, Uluçay S, Huebner A, Kasırga E (2014) Triple A syndrome with clinical and genetic findings: a case report. Çocuk Sağlığı ve Hastalıkları Dergisi 57:195–199
3. Brown B, Agdere L, Muntean C, David K (2016) Alacrima as a harbinger of adrenal insufficiency in a child with Allgrove (AAA) syndrome. Am J Case Rep 17:703–706. https://doi.org/10.12659/AJCR.899546
4. Dumić M, Barišić N, Rojnić-Putarek N, Kušec V, Stanimirović A, Koehler K, Huebner A (2011) Two siblings with triple A syndrome and novel mutation presenting as hereditary polyneuropathy. Eur J Pediatr 170(3):393–396. https://doi.org/10.1007/s00431-010-1314-4
5. Dumic M, Barišic N, Kusec V, Stingl K, Skegro M, Stanimirovic A, Koehler K, Huebner A (2012) Long-term clinical follow-up and molecular genetic findings in eight patients with triple a syndrome. Eur J Pediatr 171(10):1453–1459. https://doi.org/10.1007/s00431-012-1745-1
6. Goizet C, Catargi B, Tison F, Tullio-Pelet A, Hadj-Rabia S, Pujol F, Lagueny A, Lyonnet S, Lacombe D (2002) Progressive bulbospinal amyotrophy in triple A syndrome with AAAS gene mutation. Neurology 58(6):962–965. https://doi.org/10.1212/WNL.58.6.962
7. Grant DB, Barnes ND, Dumic M, Ginalska-Malinowska M, Milla PJ, von Petrykowski W, Rowlatt RJ, Steendijk R, Wales JH, Werder E (1993) Neurological and adrenal dysfunction in the adrenal insufficiency/alacrima/achalasia (3A) syndrome. Arch Dis Child 68(6):779–782. https://doi.org/10.1136/adc.68.6.779
8. Guran T, Buonocore F, Saka N, Ozbek MN, Aycan Z, Bereket A, Bas F, Darcan S, Bideci A, Guven A, Demir K, Akinci A, Buyukinan M, Aydin BK, Turan S, Agladioglu SY, Atay Z, Abali ZY, Tarim O, Catli G, Yuksel B, Akcay T, Yildiz M, Ozen S, Doger E, Demirbilek H, Ucar A, Isik E, Ozhan B, Bolu S, Ozgen IT, Suntharalingham JP, Achermann JC (2016) Rare causes of primary adrenal insufficiency: genetic and clinical characterization of a large nationwide cohort. J Clin Endocrinol Metab 101(1):284–292. https://doi.org/10.1210/jc.2015-3250
9. Hallal C, Kieling CO, Nunes DL, Ferreira CT, Peterson G, Barros SG, Arruda CA, Fraga JC, Goldani HA (2012) Diagnosis, misdiagnosis, and associated diseases of achalasia in children and adolescents: a twelve-year single center experience. Pediatr Surg Int 28(12):1211–1217. https://doi.org/10.1007/s00383-012-3214-3
10. Handschug K, Sperling S, Yoon SJ, Hennig S, Clark AJ, Huebner A (2001) Triple A syndrome is caused by mutations in AAAS, a new WD-repeat protein gene. Hum Mol Genet 10(3):283–290. https://doi.org/10.1093/hmg/10.3.283
11. Houlden H, Smith S, De Carvalho M, Blake J, Mathias C, Wood NW, Reilly MM (2002) Clinical and genetic characterization of families with triple A (Allgrove) syndrome. Brain 125(12):2681–2690. https://doi.org/10.1093/brain/awf270
12. Milenkovic T, Zdravkovic D, Savic N, Todorovic S, Mitrovic K, Koehler K, Huebner A (2010) Triple A syndrome: 32 years experience of a single centre (1977-2008). Eur J Pediatr 169(11):1323–1328. https://doi.org/10.1007/s00431-010-1222-7
13. Misgar RA, Pala NA, Ramzan M, Wani AI, Bashir MI, Laway BA (2015) Allgrove (triple A) syndrome: a case report from the Kashmir Valley. Endocrinol Metab (Seoul) 30(4):604–606. https://doi.org/10.3803/EnM.2015.30.4.604
14. Papageorgiou L, Mimidis K, Katsani KR, Fakis G (2013) The genetic basis of triple A (Allgrove) syndrome in a Greek family. Gene 512(2):505–509. https://doi.org/10.1016/j.gene.2012.10.008
15. Phillip M, Hershkovitz E, Schulman H (1996) Adrenal insufficiency after achalasia in the triple-A syndrome. Clin Pediatr (Phila) 35(2):99–100. https://doi.org/10.1177/000992289603500208
16. Prasad R, Metherell LA, Clark AJ, Storr HL (2013) Deficiency of ALADIN impairs redox homeostasis in human adrenal cells and inhibits steroidogenesis. Endocrinology 154(9):3209–3218. https://doi.org/10.1210/en.2013-1241
17. Prpic I, Huebner A, Persic M, Handschug K, Pavletic M (2003) Triple A syndrome: genotype-phenotype assessment. Clin Genet 63(5):415–417. https://doi.org/10.1034/j.1399-0004.2003.00070.x
18. Storr HL, Kind B, Parfitt DA, Chapple JP, Lorenz M, Koehler K, Huebner A, Clark AJ (2009) Deficiency of ferritin heavy-chain nuclear import in triple a syndrome implies nuclear oxidative damage as the primary disease mechanism. Mol Endocrinol 23(12):2086–2094. https://doi.org/10.1210/me.2009-0056
19. Tullio-Pelet A, Salomon R, Hadj-Rabia S, Mugnier C, de Laet MH, Chaouachi B, Bakiri F, Brottier P, Cattolico L, Penet C, Bégeot M, Naville D, Nicolino M, Chaussain JL, Weissenbach J, Munnich A, Lyonnet S (2000) Mutant WD-repeat protein in triple-A syndrome. Nat Genet 26(3):332–335. https://doi.org/10.1038/81642
20. Weber A, Wienker TF, Jung M, Easton D, Dean HJ, Heinrichs C, Reis A, Clark AJ (1996) Linkage of the gene for the triple A syndrome to chromosome 12q13 near the type II keratin gene cluster. Hum Mol Genet 5(12):2061–2066. https://doi.org/10.1093/hmg/5.12.2061
21. Wente SR, Rout MP (2010) The nuclear pore complex and nuclear transport. Cold Spring Harb Perspect Biol 2:a000562