Novel Insights from Clinical Practice

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Late-Onset Triple A Syndrome: A Risk of Overlooked or Delayed Diagnosis and Management

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Established Facts

- Triple A syndrome generally manifests during childhood, mostly during the first decade.
- Adult onset of the disease is very rare.
- There is a risk of delayed diagnosis.

Novel Insights

- Late-onset form of triple A syndrome should be considered as possible and adult onset may be a confounding factor for the diagnosis, due to its rarity.
- The diagnosis of triple A syndrome should be checked also in adult patients with one or more clinical signs and symptoms of the disease.
- Increasing the awareness on late onset triple A syndrome among physicians may prevent overlooking and undermanaging the disease.
- An adequate multidisciplinary clinical approach is advocated in these patients, especially in adulthood.

Key Words
ALADIN · Allgrove syndrome · Glucocorticoid deficiency · Nuclear pore complex · Nucleoporin

Abstract
Background/Aims: A 33-year-old man was referred for the first time to the Division of Neurology because of the presence and progression of neurological symptoms. Dysphagia, weakness, reduced tear production, and nasal speech

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were present. In order to point the attention of late-onset triple A syndrome we describe this case and review the literature. ***Methods:*** Hormonal and biochemical evaluation, Schirmer test, tilt test and genetic testing for *AAAS* gene mutations. ***Results:*** Late-onset triple A syndrome caused by a novel homozygous missense mutation in the *AAAS* gene (A167V in exon 6) was diagnosed at least 17 years after symptom onset. ***Conclusions:*** The association between typical signs and symptoms of triple A syndrome should suggest the diagnosis even if they manifest in adulthood. The diagnosis should be confirmed by Schirmer test, endocrine testing (both basal and dynamic), genetic analysis, and detailed gastroenterological and neurological evaluations. Awareness of the possible late onset of the disease and of diagnosis in adulthood is still poor among clinicians, the acquaintance with the disease is more common among pediatricians. The importance of an adequate multidisciplinary clinical approach, dynamic testing for early diagnosis of adrenal insufficiency and periodical reassessment of adrenal function are emphasized.

Introduction

The association among familial glucocorticoid deficiency due to ACTH insensitivity, achalasia of the cardia, alacrima and autonomic dysfunction was firstly described in 1978 by Allgrove et al. [1] in two pairs of siblings (aged 4–6 years). This rare condition is also called triple A syndrome (adrenal dysfunction/alacrima/achalasia), and may be associated with autonomic nervous system failure, neurological disorders (autonomic failure and/or peripheral neuropathy, abnormal functioning of peripheral motor and sensory fibers), impaired cognitive function, mental retardation and dementia [1, 2].

The linkage of the triple A syndrome locus to markers on chromosome 12q13 (AS; MIM No. 231550) [2–5], and the effect of mutations in the gene encoding ALADIN (AAAS; *605378) have been demonstrated. ALADIN is a protein that belongs to the WD tryptophane-aspartic acid repeat-containing protein (WD) family [3]. The function of the ALADIN protein is not clear, but it could be shown that it is a component of the nuclear pore complex (NPC) of cells [2, 3]. The inheritance of the disease is autosomal recessive [2–5] and it occurs in childhood with a high rate of sudden death due to acute crisis of hypoglycemia when the disease is not recognized [4–8]. Furthermore, several reports described the occurrence of the syndrome in adulthood [9–12], and Kimber et al. [11] provided interesting evidence on the existence of a subgroup of patients with a less severe pediatric clinical presentation and course of disease.

Here we report a case of late-onset triple A syndrome in an adult Italian subject with a novel mutation in the *AAAS* gene and provide a review of the literature on late-onset occurrence of the disease [9–12], paying particular attention to the progressive nature of the manifestations in adulthood. The aim is to add information to the small literature on delayed-onset forms and to reinforce the concept of a possible occurrence of the disease in adulthood, providing a useful reminder to the endocrine community on the difficulties in diagnosis.

Case Report

A 33-year-old man was referred for the first time to the Division of Neurology because of the presence and the progressive advancement of neurological symptoms in the previous 3 years and achalasia. The patient's family history was uneventful from the viewpoint of gastroenterological, endocrinological and neurological diseases. The patient's past medical history involved several periods of hospitalization, without any precise diagnosis. Since the age of 8 years, some mild gastrointestinal symptoms (episodes of nausea and rare vomiting) were present, but they did not require medical consultation and had no significant consequences for his wellbeing. At the age of 16, due to progressive dysphagia, nausea, vomiting and weight loss, the patient underwent a standard X-ray with barium contrast leading to the diagnosis of idiopathic mega-esophagus. The patient was treated surgically with extramucosal Heller's myotomy, resulting in improved symptoms and an 11-year disease-free period.

At the age of 27 years, the patient again started to complain of dysphagia, followed by loss of muscle strength with preferential distal muscular atrophy. During hospitalization in a gastroenterological unit, the diagnosis of achalasia was confirmed by means of endoscopic and manometric evaluations. Subsequent evaluations of fasting glucose showed a trend towards values at the lower end of the normal range (59, 67, 73 mg/dl) without a history of symptoms related to hypoglycemia; moreover, low 24-hour urinary cortisol levels (62, normal range 92–473 μg/24 h) were measured, together with normal serum cortisol (14 μg/dl) and ACTH (15 pg/ml) at 8:00 a.m. and normal values of natremia and kalemia. Notwithstanding these biochemical data, endocrinological counseling at that time excluded adrenal insufficiency and the absence of clinical signs did not prompt further examinations.

At the age of 30, the patient needed a further hospitalization in a neurological unit because of muscular weakness associated with rhinolalia, perioral fasciculations, atrophy and fasciculations of the tongue, widespread muscular hypotrophy and weak Achilles tendon reflexes. Motor neuron disease was diagnosed based on the presence of a normal brain MRI and on electromyography/electroneurography, showing both signs of mixed axonal-demyelinating sensorimotor polyneuropathy and muscle denervation in the limbs and bulbar musculature.

Table 1. Anthropometric, hormonal and nutritional parameters in a 33- year-old patient with triple A syndrome

		Normal range
Anthropometric parameters		
Height, cm	170	–
Weight. kg	40	–
BMI	13.8	18.5–24.9
Total body fat (DXA), %	8.2	14–25
DXA parameters		
BMD femoral neck, g/cm^2	0.665	–
t-score	–3.1	<2
BMD (L2–L4), g/cm^2	0.994	–
t-score	–1.8	<2
Total fat body mass, %	8.2	–
Total lean body mass, %	91.8	–
Hormonal measurements[1]		
Basal serum cortisol, μg/dl	14.4	5.5–25
Serum cortisol, μg/dl, peak 30 min after ACTH	13.7	>18
Basal serum DHEA-S, μg/ml	0.68	0.8–5.6
Serum DHEA-S, μg/ml, peak 30 min after ACTH	0.7	–
Basal serum ACTH	13.2	9–52
24-hour urinary cortisol, μg/24 h	47	7–152
25-OH vitamin D, ng/ml	9	11–68
Fasting insulin, mIU/ml	2.1	2.5–20
Fasting glucose, mg/dl	70	50–110
TSH, IU/l	1.42	0.35–4.5
FT3, pg/ml	3.4	1.7–4.2
FT4, pg/ml	10.6	6.1–16.7
Prolactin, ng/ml	8	2.1–17.7
LH, IU/l	4	1.4–8.9
FSH, IU/l	1.7	1.7–6.9
Testosterone, ng/dl	370	360–900
Supine/orthostatic renin, μU/ml	24.3/37.9	2.4–29/3.3–41
Supine/orthostatic aldosterone, pg/ml	54.3/136.4	10–150/35–300
24-hour urinary aldosterone, μg/24 h	8.8	2.8–30
Biochemical parameters[1]		
Calcium, mEq/l	4.39	4.2–5.5
Phosphate, mg/dl	2.91	2.5–5.9
Total cholesterol, mg/dl	148	140–250
HDL-cholesterol, mg/dl	40	>45
LDL-cholesterol, mg/dl	89	0–150
Nutritional, hormonal and biochemical parameters		
Triglycerides, mg/dl	66	<175
Vitamin B_{12}, pg/ml	664	200–900
Folic acid, ng/ml	1.94	4–20
Iron, ug/dl	28	60–160
IGF-1 ng/ml	101	98–362

[1] All values refer to serum concentrations except for urinary cortisol.

At the age of 32, a progressive bilateral sight loss became evident. Electroretinography was normal, but visual evoked potentials were markedly altered bilaterally. Moreover, the patient displayed a history of symptomatic hypotension.

During the last hospitalization (aged 33) the patient, seen by us for the first time, exhibited marked dysphagia with modest generalized weakness and tiredness, occurring mainly late in the afternoon. After specific questioning, the patient reported frequent episodes of hyperhydrosis and persistently reduced tear production over the last few years. Poor general condition and malnutrition were present (table 1). Physical examination showed facial characteristics of triple A syndrome: elongated face, narrow upper lip, nasal speech, bilateral pectus carinatum with central cavus and scoliosis, atrophy of the tongue, and enamel hypoplasia of the teeth. The muscles were atrophic, especially the lower and upper limb muscles.

On the basis of both the clinical and medical history, the diagnosis of triple A syndrome suggested itself and the patient underwent endocrine/metabolic, neurological and genetic evaluations.

Results

The neurological examination showed a worsening of some preexisting signs, together with dysphonia, distal dysesthesia and hyperesthesia in lower limbs, weak Achilles tendon reflexes with other deep tendon reflexes being brisk, spastic gait, and bilateral atrophy of the optic discs. Somatosensory evoked potentials were normal.

The examination of autonomic nervous system reflexes indicated the involvement of the sympathetic nervous system; the tilt test showed evident orthostatic hypotension with acrocyanosis and a compensatory increase in heart rate.

The Schirmer test disclosed severe bilateral hypolacrima.

Endocrinological examinations revealed that the basal serum levels of ACTH, cortisol, and 24-hour urinary cortisol were within the normal range, but 30 min after a 250-μg i.v. bolus of $ACTH^{1-24}$ Cosyntropin (Cortrosyn®, Organon, West Orange, N.J., USA) the cortisol levels failed to rise above the normal 18 μg/dl cutoff (table 1), leading to the diagnosis of adrenal insufficiency. Hyponatriemia and hyperkalemia were absent. Basal supine serum renin and aldosterone were normal and both increased during orthostatism. 24-hour urinary aldosterone was at the lower end of the normal range. Moreover, a CT scan of the abdomen revealed a pattern of mild bilateral hypoplasia of the adrenal glands. No other endocrinological abnormalities were present (table 1). Metabolic evaluation showed that the patient was severely underweight (40 kg) with a BMI of 13.8 kg/m^2. Total body fat measured by DXA (Lunar DPX-L®, Lunar Corp., Madison, Wisc., USA) was very low (8.2% of the total body composition; table 1). Femoral osteoporosis was diagnosed on the basis of reduced bone mineral density, while osteopenia was seen at the lumbar level (L2–L4; table 1). A slight normocytic anemia with serum folate, iron, vitamin D and IGF-1 below the normal ranges, and a trend towards lower levels (although within normal ranges) of fasting serum glucose, triglycerides and serum insulin (table 1) were all most likely due to both dysphagia-related malnutrition and achalasia-related malabsorption.

The DNA analysis allowed us to identify a novel homozygous C>T transition at bp 500 in exon 6 of the *AAAS* gene resulting in a change of alanine at amino acid position 167 into valine of the ALADIN protein (p.Ala167Val; table 2; fig. 1). As expected, the parents and the healthy brother were heterozygous carriers for this mutation (fig. 1). The mutation in the transfected HeLa cells resulted in a GFP-$ALADIN^{A167V}$ protein being mislocalized from the NPC to the cytoplasm (fig. 2). Differences in the species-specific ALADIN protein sequences compared to the human protein were detected and are summarized in figure 3. Percentages demonstrate homology to the WD-repeat motif and homology of the entire amino acid sequence compared to the human ALADIN protein (fig. 3).

Discussion

Diagnosis

The association between familial glucocorticoid deficiency, achalasia of the cardia and alacrima was described for the first time in 1978 by Allgrove et al. [1]. This rare condition is now commonly known as triple A syndrome (adrenal dysfunction/alacrima/achalasia) and the linkage of the triple A syndrome locus to markers on chromosome 12q13 (AS; MIM No. 231550) [2] is well known. The inheritance of the disease is autosomal recessive [2–5] and the disease generally manifests during childhood, mostly during the first decade [6]. The mean age at onset and diagnosis is about 6–8 years or less [2, 7, 8], the high rate of sudden deaths being due to acute crises of hypoglycemia when the disease is not recognized [4–6]. However, clinical features may uncommonly manifest over a variable period of time [3–7] and the adult onset of the disease is rare. As reviewed here, only 8 cases of triple A syndrome have been diagnosed during adulthood [4, 9–12], some of which in late adolescence [4, 9–12] (table 2); only a small number of these had the diagnosis confirmed

Table 2. Genetic characteristics, clinical pattern and progression of the disease in patients with triple A syndrome diagnosed in adulthood (comprising the case presented here)

Reference	Sex	Age at onset years	Age at diagnosis years	Gene defects (*AAAS* gene mutations)	Transcript(s)	Progression of the disease					Associated features
						1st manifestation	2nd manifestation	3rd manifestation	4th manifestation	5th manifestation	
Moore et al. [9] 1991	F	13	23	n.p.	n.p.	Achalasia, muscle weakness, alacrima (13 years)	Muscle weakness	Adrenal insufficiency (29 years)	–	–	Moderate mental retardation
Bentes et al. [10] 2001 Houlden et al. [4] 2002	M	25	35	Homozygote c.938T>C (exon 10)	Val313Ala	Achalasia (25 years)	Lower limb weakness (30 years)	Autonomic failure (33 years)	Alacrima, erectile dysfunction (35 years)	Borderline adrenal insufficiency (36 years)	Dysphonia, dysarthria, dysphagia
Houlden et al. [4] 2002	M	16	48	Compound heterozygote (1) c.43C>A (exon 1) (2) c.1066_1067delCT (exon 11)	(1) Glu14fs (2) Leu356fs	Lower limb weakness	Achalasia, Alacrima	Partial adrenal insufficiency	–	–	–
Houlden et al. [4] 2002	M	12	37	Compound heterozygote (1) c.787T>C (exon 8) (2) c.1191insA (exon 13)	(1) Ser263Pro (2) Glu398fs	Lower limb weakness	Achalasia, Alacrima	Borderline adrenal insufficiency	–	–	–
Kimber et al. [11] 2003	M	9	40	Compound heterozygote (1) c.464G>A (exon 6) (2) c.972G>A (exon 10)	(1) Arg155His (2) Trp324X	Achalasia (9 years)	Progressive muscular weakness and gait, ataxia (32–34 years)	Alacrima, erectile dysfunction, regional hyperhidrosis (34 years)	Dysarthria, orthostatic hypotension	–	–
Kimber et al. [11] 2003	F	24	43	n.p.	n.p.	Achalasia (24 years)	Paraesthesiae, mild palatal weakness (34 years)	Gait disturbances, orthostatic hypotension, regional hyperhidrosis (37 years)	Blackouts, dysphagia (43 years)	–	Gonadotropic dysfunction
Kimber et al. [11] 2003	M	20	60	n.p	n.p.	Gait disturbances (20 years)	Achalasia (28 years)	Blackouts related to sudden postural change (60 years)	Erectile dysfunction, regional hyperhidrosis	–	–
Pedreira et al. [12] 2004	M	17	37	n.p.	n.p.	Achalasia, alacrima (17 years)	Generalized weakness, muscle weakness (31 years)	Erectile dysfunction and ejaculatory failure (31–35 years)	Lethargy, collapse with hypotension (35 years)	–	–
Present case report	M	16	30	Homozygote c.500C>T (exon 6)	Ala167Val	Achalasia (16 years)	Muscle weakness (27 years)	Adrenal insufficiency (33 years)	–	–	Bilateral atrophy of the optic discs

n.p.= Not performed. The nomenclature is in accordance to den Dunnen (http://www.hgvs.org/mutnomen/).

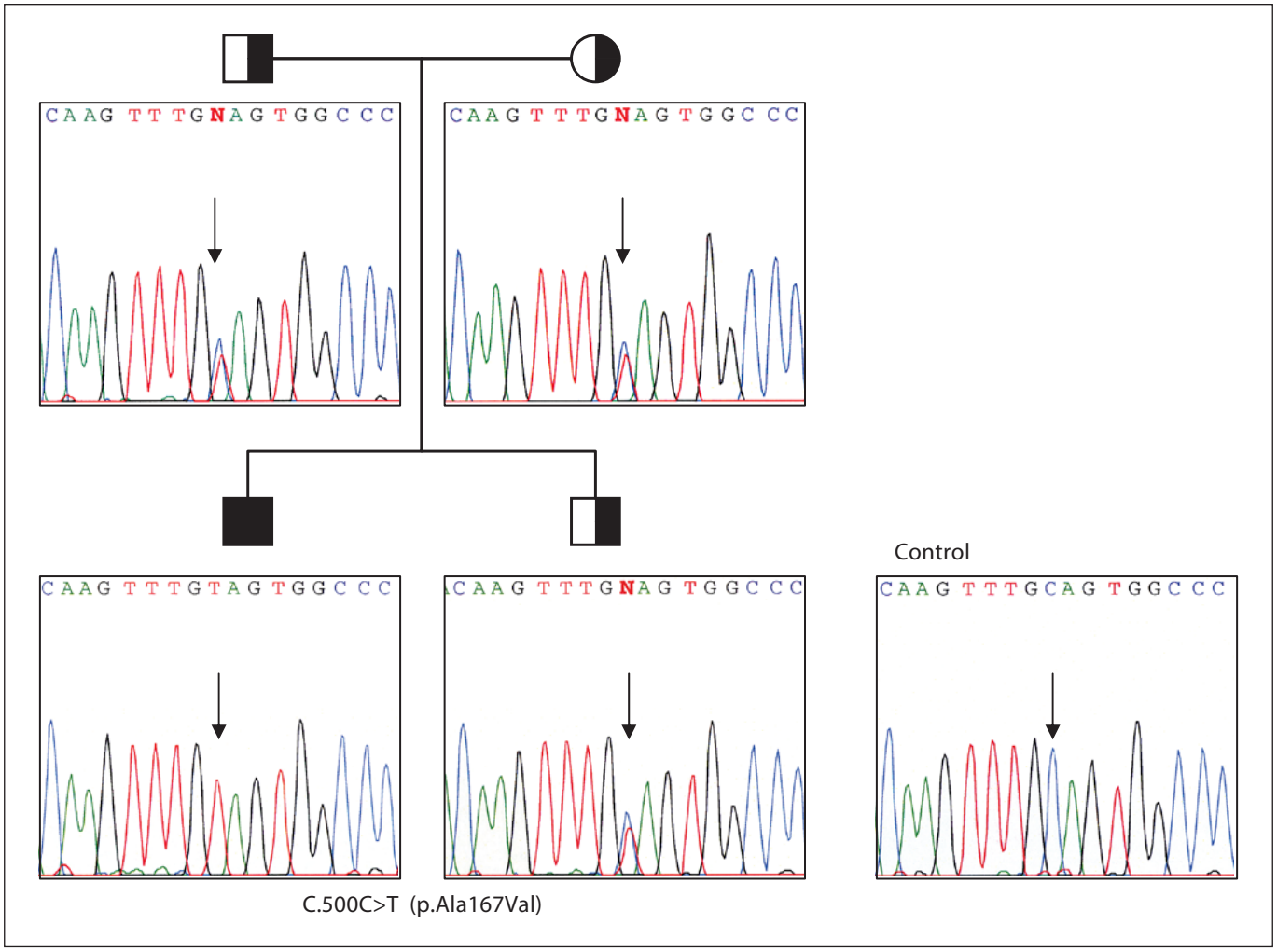

Fig. 1. *AAAS* mutation in the index patient with triple A syndrome. Sequence chromatograms of the patient, his healthy brother and parents compared with the respective wild-type (control) sequence. The arrow indicates the nucleotide altered by the mutation that occurred at C.500C>T in exon 6 of the *AAAS* gene (GenBank accession No. NH_015665). The DNA analysis was performed in accordance with standard protocols, as previously reported [3]. The nomenclature follows den Dunnen (http://www.hgvs.org/mutnomen/).

by a detailed molecular genetic analysis [4, 10, 11], with the diagnosis often only inferred from clinical features [9, 12] (table 2).

The pathophysiological basis of triple A syndrome is poorly understood and the progressive involvement of several organs and systems hinders the understanding of the natural history of the disease. The first step in the development of the disease is a mutation in the gene encoding ALADIN (*AAAS*; *605378) [2], a protein belonging to the WD family [3]. The function of the ALADIN protein is not clear, but it can be shown that it is a component of the NPC of cells [13]. NPCs are involved in cell growth and differentiation and are crucial sites for macromolecule translocation between the nucleus and the cytoplasm [13]. Normally, wild-type ALADIN is located to the NPCs, while mutated proteins that induce triple A syndrome are mislocalized to the cytoplasm [13]. The wide spectrum of clinical features in subjects with triple A mutations reflects the complex function (cell division control, signal transduction, RNA processing, cytoskeleton assembly, vesicular trafficking and protein interactions) of ALADIN [13]. Since Alanine 167 is highly conserved among species (fig. 3) and is located in a motif responsible for β-sheet folding of the WD the mutation observed in this

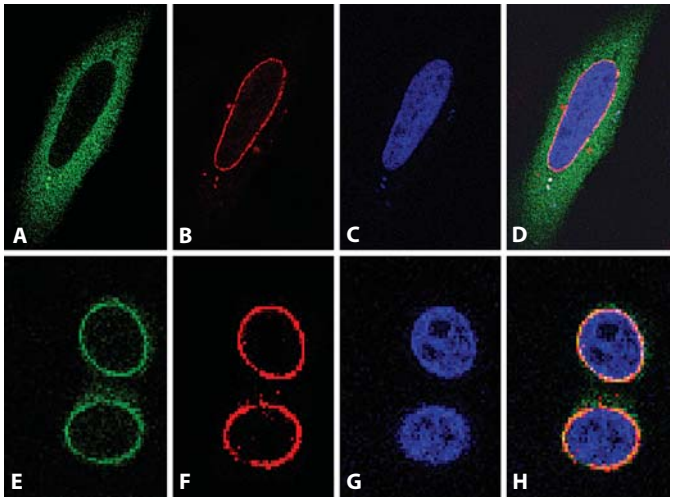

Fig. 2. Cellular localization of the wild-type and Ala167Val mutant ALADIN. While wild-type ALADIN is normally located to the nuclear pore complex (**E**), the mutant GFP-ALADIN^{A167V} is mislocalized to the cytoplasm (**A**, green). **B**, **F** The localization of Nup62 (red). **C**, **G** DAPI staining of the nucleus (blue). **D**, **H** An overlay of figures **A–C** and **E–G**, respectively. **H** Colocalization to the nuclear membrane (yellow). **D** The lack of a yellow ring proves the absence of GFP-ALADIN^{A167V} targeting at the nuclear pore complexes. The aberrant protein is mislocalized from the NPC to the cytoplasm in transfected HeLa cells as it happens when an ALADIN gene mutation is present [13].

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Homo sapiens	546 aa	NP_056480		WSSCCLRVFAWHPHTNKF**A**VALLDDSVRVYN
Pan troglodytes	519 aa	XP_522403*	(100%/92%)	WSSCCLRVFAWHPHTNKF**A**VALLDDSVRVYN
Bos taurus	495 aa	XP_583023*	(100%/96%)	WSSCCLRVFAWHPHTNKF**A**VALLDDSVRVYN
Canis familiaris	591 aa	XP_849797*	(97%/94%)	WSSCCLRVFAWHPHTNKF**A**VALLDDSIRVYN
Mus musculus	546 aa	NP_700465	(97%/94%)	WSSCCLRVFAWHPHTNKF**A**VALLDDSIRVYN
Rattus norvegicus	546 aa	XP_001067255*	(97%/92%)	WSSCCLRVFAWHPHTNKF**A**VALLDDSIRVYN
Gallus gallus	423 aa	XP_423852*	(81%/56%)	WAGCSIRAFAWHPHTSKF**A**VALLDDSVRVYN
Xenopus laevis	523 aa	AAH77988	(71%/64%)	WADCPLRAFAWHPHTYKF**A**LALLDDSIRIYT
Danio rerio	499 aa	NP_998390	(64%/56%)	WSDSAVRSFSWHPHTDKF**A**VALLDDSIKIYK
Tribolium castaneum	494 aa	XP_969843*	(45%/33%)	WANNTIKCIAWHLHNSRL**A**VATCDDSVRIYC
Strongylocentrotus purpuratus	472 aa	XP_787398*	(45%/45%)	WQDSEIRAFAWHQHTNKC**A**VAWKDNTIKIFI

Fig. 3. Species-specific sequence homology of the human arginine 167. Asterisks indicate a predicted or partially predicted amino acid sequence. Amino acids in gray show differences in the species-specific ALADIN protein sequences compared to the human protein. The affected amino acid A167 is highlighted in bold face. Residues marked with – – – are predicted in humans to fold into β-sheets. Percentages demonstrate homology to the WD-Repeat motif and homology of the entire amino acid sequence compared to the human ALADIN protein.

patient suggests that this residue might be important for the normal function of the ALADIN protein.

Even in the typical childhood occurrence [1, 6, 7] of triple A syndrome, there is a risk of delayed diagnosis, as previously stated by other authors (table 2) [4, 9–12]. Due to paucisymptomatic manifestation during childhood and adolescence and the slow progression of the disease during adulthood, a delay in diagnosis may occur, as demonstrated by the reported case, with the clinical diagnosis postulated at 33 years and subsequently confirmed by genetic and biomolecular analyses. Adulthood may be a further confounding factor, the disease being generally diagnosed and managed by pediatricians, but in clinical practice, the disease should be taken into consideration in adult patients with one or more clinical signs and symptoms of the disease [4, 9–12]. Diagnosis of the disease is uncommon during adolescence and adulthood, and it is at a major risk of being overlooked and delayed, as in this case.

Neurological disorders (autonomic failure and/or peripheral neuropathy, abnormal functioning of peripheral motor and sensory fibers), impaired cognitive functions,

mental retardation and dementia may all be part of the syndrome [2, 6]. Several other concomitant features may involve different organ systems such as bone (premature osteoporosis), skin (palmoplantar hyperkeratosis, cutis anserina and impaired wound healing), and oral cavity (xerostomia and tongue abnormalities) [2, 6]. Generally, alacrima is the first and most consistent symptom which can, however, be overlooked [5]. Achalasia represents the most precocious symptom, which leads to medical consultation not only in children [5, 8], but also in subjects with the late-onset disease (table 2) [4, 9–12].

Adrenal insufficiency and neurological impairment can become clinically evident after a variable period of time ranging from 5 to more than 10 years after disease onset [4, 9–12] (table 2). As in the present case, neurological symptoms may progress slowly and the course of hypocortisolism may be subclinical, confirming that these disease features may be overlooked easily [4, 9–12]. Autonomic dysfunction was present in one of the eight cases of late-onset triple A syndrome [4], but in the other subjects the symptoms (orthostatic hypotension and hyperhidrosis) provided cause for strong suspicion [4, 9, 11, 12] (table 2).

Severe hypoglycemic episodes due to hypocortisolism have been described [6] in several previous reports and sudden deaths have been documented in triple A syndrome [5–7], as well as suggested by the family history of some affected subjects (i.e., probably unrecognized cases of affected relatives) [11]. In fact, the onset of adrenocortical impairment usually occurs before puberty even though preservation of cortisol secretion into the third decade has been reported [9]. Our patient never complained of symptoms related to severe hypoglycemia, but upon investigation, fasting glucose levels of less than 70 mg/dl were found relative to the several periods of hospitalization. This may have been due to subclinical adrenal insufficiency, present for several years before the diagnosis. The diagnosis of hypocortisolism is frequently delayed in patients with adrenal insufficiency, because of the subtle nature of the clinical complaints (weakness, tiredness, dizziness and slow weight loss) and several concomitant and confounding features (e.g. malnutrition) as in this case. Such a delay in the diagnosis of adrenal insufficiency emphasizes the need for a correct assessment of the adrenal function in any young subject with achalasia or alacrima. In clinical practice, triple A-related adrenal insufficiency cannot be diagnosed only on the basis of the endocrine basal serum evaluation (ACTH and cortisol); it also requires dynamic tests [14], as in the investigation of the hypothalamic-pituitary adrenal axis in other clinical conditions [15].

The patient's clinical features should lead physicians to check the diagnosis of triple A syndrome, also in adult patients. The Schirmer test is a simple and reliable test for alacrima, but the diagnosis should be confirmed by genetic analysis. Endocrinological evaluation should be based on both basal and dynamic measurements and hypocortisolism should be periodically controlled as it may develop late in the disease. Metabolic, gastroenterological and neurological evaluations are mandatory to guarantee the patient's wellbeing.

Treatment and Management

Acquaintance with the disease could allow earlier diagnosis and therefore effective prevention of potentially life-threatening complications due to hypocortisolism in adult patients with suspected triple A syndrome. It seems that, as in children [6], also in these cases of late-onset triple A syndrome (table 2) [1, 4, 9–12] adrenal insufficiency occurred after other clinical manifestations, and that it may be not have been present or may have been overlooked in evaluations performed some years before [9]. In our patient, the diagnosis of adrenal insufficiency followed that of achalasia by about 20 years.

After the endocrinological evaluation, replacement therapy with 37.5 mg/day cortisone acetate was initiated. Additionally, although no clear mineralocorticoid deficiency was present, the patient was started on mineralocorticoid therapy (0.1 mg/day fludrocortisone acetate) in view of the symptomatic continuous hypotension, with subsequently markedly improved subjective feelings and blood pressure parameters.

In order to improve the nutritional condition, both simple feeding suggestions (preference for 'comminuted' foods, frequent meals, soft or semi-liquid foods) and a diet of 2,090 kcal/day were provided. Iron, folate, vitamin B_{12}, calcium and vitamin D_3 supplementation to the diet was strongly recommended. Treatment led to improved subjective feelings, blood pressure parameters and weight.

Conclusions

We report the complex clinical course of a 33-year-old man with late-onset triple A syndrome, the diagnosis of which was delayed and the disease overlooked and undermanaged probably as a consequence of its unusual manifestation in adulthood.

As an increasing number of cases are being identified, the possible occurrence of triple A syndrome during

adulthood should be taken into consideration in clinical practice when one of the main signs or symptoms or more than one of the other symptoms are present, in order to avoid a delay in diagnosis and undermanagement of this rare form of the disease [4, 9–12] (table 2). Awareness of the possible late onset of the disease as well as the possibility of a diagnosis in adulthood is still poor among endocrinologists, internists, gastroenterologists and neurologists as previously suggested [12], the acquaintance with the disease remaining more common among pediatricians. Thus, the diagnostic work-up carried out suggests that the wide spectrum of clinical conditions requires a multidisciplinary approach to the disease, especially in adulthood, involving different clinical skills for the diagnosis, the follow-up and the therapeutic decisions. From this viewpoint, the follow-up should also include a periodical endocrinological evaluation by basal and dynamic testing.

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Contribution Statement for Each Author

All the authors contributed substantially to the writing and to the critical revision of the entire manuscript. All the authors approved its final version. Andrea Salmaggi first examined the patient and supposed the diagnosis of triple A syndrome. Vincenzo Rochira and Andrea Salmaggi wrote the first draft of the manuscript. Angela Huebner, Manuela Krumbholz and Katrin Koehler performed the genetic and biomolecular analyses. Andrea Salmaggi, Chiara Pantaleoni, Gabriella de Joanna and Francesca del Sorbo performed the neurological examinations. Lucia Zirilli coordinated literature searches and analyses. Vincenzo Rochira and Lucia Zirilli performed the endocrine and metabolic evaluations and critically reviewed the literature.

References

1 Allgrove J, Clayden GS, Grant DB, Macaulay JC: Familial glucocorticoid deficiency with achalasia of the cardia and deficient tear production. Lancet 1978;1:1284–1286.

2 Online Mendelian Inheritance in Man. OMIM (TM). Bethesda, Center for Medical Genetics, Johns Hopkins University, and National Center for Biotechnology Information, National Library of Medicine, 1999. URL: http://www.ncbi.nlm.nih.gov/entrez/dispomim.cgi?id=231550.

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 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.

5 Prpic I, Huebner A, Persic M, Handschug K, Pavletic M: Triple A syndrome: genotype-phenotype assessment. Clin Genet 2003;63:415–417.

6 Clark AJ, Weber A: Adrenocorticotropin insensitivity syndromes. Endocr Rev 1998;19:828–843.

7 Geffner ME, Lippe BM, Kaplan SA, Berquist WE, Bateman JB, Paterno VI, Seegan R: Selective ACTH insensitivity, achalasia, and alacrima: a multisystem disorder presenting in childhood. Pediatr Res 1983;17:532–536.

8 Grant DB, Dunger DB, Smith I, Hyland K: Familial glucocorticoid deficiency with achalasia of the cardia associated with mixed neuropathy, long-tract degeneration and mild dementia. Eur J Pediatr 1992;151:85–89.

9 Moore PS, Couch RM, Perry YS, Shuckett EP, Winter JS: Allgrove syndrome: an autosomal recessive syndrome of ACTH insensitivity, achalasia and alacrima. Clin Endocrinol 1991;34:107–114.

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 Kimber J, McLean BN, Prevett M, Hammans SR: Allgrove or 4 'A' syndrome: an autosomal recessive syndrome causing multisystem neurological disease. J Neurol Neurosurg Psychiatr 2003;74:654–657.

12 Pedreira CC, Zacharin MR: Allgrove syndrome: when a recognizable paediatric disorder occurs in adulthood. Med J Aust 2004;180:74–75.

13 Cronshaw JM, Matunis MJ: The nuclear pore complex protein ALADIN is mislocalized in triple A syndrome. Proc Natl Acad Sci USA 2003;100:5823–5827.

14 Salehi M, Houlden H, Sheikh A, Poretsky L: The diagnosis of adrenal insufficiency in a patient with Allgrove syndrome and a novel mutation in the ALADIN gene. Metabolism 2005;54:200–205.

15 Nieman KL: Dynamic evaluation of adrenal hypofunction. J Endocrinol Invest 2003;26:74–82.