Triple-A Syndrome (TAS): an in-depth overview on genetic and phenotype heterogeneity

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Abstract

Triple-A Syndrome (TAS) is a rare autosomal recessive disorder characterized by three cardinal symptoms: alacrimia, achalasia and adrenal insufficiency due to ACTH insensitivity. Various progressive neurological abnormalities and skin changes have been described in association with the syndrome. The disease is caused by mutation in the AAAS gene on chromosome 12q13. Mutations in AAAS were identified in more than 90% of individuals and families with TAS. The protein encoded by AAAS was termed ALADIN and is part of the WD repeat family of proteins, that have been found to be involved in many different functions such as protein-protein interaction, RNA processing, cytoskeleton assembly, control of cell division, signal transduction and apoptosis. Immunohistochemical analysis showed that mutated or truncated ALADIN localizes to the cytoplasm rather than to the nuclear pore complex. The exact function of ALADIN and the mechanisms that lead to the ACTH-resistant adrenal phenotype remains largely unknown. Nonetheless, recent studies provided some insights on the role of ALADIN as a member of the Nuclear Pore Complex not only implicated in the import of proteins involved in DNA repair and oxidative stress homeostasis but also in the strengthening of the mitotic spindle assembly. Early identification of the syndrome is challenging, given the rarity of the condition and high phenotypic heterogeneity even among members of the same family. In this review, we aim to summarize the current knowledge of clinical and molecular profile of patients with TAS and recommendations for the diagnosis, management, and follow-up of patients.
Keywords: Triple-A Syndrome, AAAS gene, Aladin, Adrenal Insufficiency, Achalasia, Alacrimia, 4A Syndrome, 5A Syndrome

Introduction

Triple-A Syndrome (TAS) is a rare autosomic recessive disorder characterized by a highly heterogeneous phenotype, which is also known as Allgrove syndrome. Indeed, TAS was first discovered by Allgrove in 1978 who reported two pairs of siblings presenting the triad of symptoms of esophageal Achalasia, Adrenal insufficiency and Alacrimia. The disease was previously thought as belonging to the Familiar Glucorticoid Deficiency syndromes due to presence of adrenocorticotropic insensitivity, although in the absence of any mutation of the ACTH receptor (also named MC2R). As a result of the combination of these three common manifestations the term Triple-A syndrome was then coined. TAS is a rare disease with a still unknown precise prevalence, mainly affecting inbred population, and with a variable phenotype of presentation. Due to its particular rarity, most of the current literature is represented by case reports. In the present review we aimed at extensively revising the known literature concerning the clinical and genetic clues of TAS. We thus provide the readers with an overview of the syndromic clinical features heterogeneity and we catalogue all known mutations, to report studies about the pathological mechanisms of AAAS gene mutations and ALADIN protein functions.

Methods
We performed literature search on PubMed for studies published up to November 2019 with the keywords “Triple-A Syndrome”, “Allgrove Syndrome”, “3A Syndrome”, “4A Syndrome”, “AAAS gene” and “ALADIN protein”. Meanwhile, we checked the references of each included paper to identify additional relevant publications.

**Inclusion Criteria for listing of mutations:**

1. Case reports, due to the rarity of the disease.
2. Original articles and single center experiences with mutations reported.

**Exclusion Criteria for Studies:**

1. Absence of genotype analysis.

**Clinical presentation**

TAS is rather well known for its high heterogeneity in symptoms, and even subjects of the same family, harboring identical variants in the *AAAS* gene, can show a different degree of clinical manifestations, thus indicating a lack of genotype-phenotype correlation. The complete triad of Achalasia, Alacrimia and Adrenal Insufficiency (Allgrove triad) may not appear together at diagnosis and so the disease is sometimes named 2A syndrome. Moreover, the disease has also been called 4A or 5A syndrome depending if neurologic manifestations and amyotrophy are included. Due to its severity, the manifestation leading to the diagnosis is usually adrenal insufficiency which lead to hypoglycemic convulsions, growth delay and skin hyperpigmentation. Nonetheless, the earliest sign of this syndrome is actually alacrimia, which is almost invariably already existent at the moment of disease presentation \(^2,3\). In fact, the clinical diagnosis of TAS is usually made through the combination of 2 manifestations out of the classic Allgrove triad, although some authors claim that even incomplete presentations, especially the recognition of alacrimia alone, are highly suspicious for this syndrome \(^3-5\). Once the
clinical manifestations have been carefully evaluated, genetic testing is important for final diagnosis. Moreover, symptoms, especially neurological disorders, may also evolve over time leading to the idea that this is a progressive disease.

*Alacrimia*

Among the three components of the common triad it has been reported that Alacrimia is the most prevalent first symptom attested in around 90-100% of the reported cases.\(^6\)\(^-\)\(^9\) Alacrimia is sometimes reported to be present from birth or noted within the first year of life.\(^10\)\(^,\)\(^11\) However, usually patients do not refer to the clinician for this specific symptom which is often reported only after direct questioning. The pathogenesis of alacrimia is probably related to a dysfunction of the autonomic nervous system in the lacrimal glands\(^2\)\(^,\)\(^12\)\(^,\)\(^13\) and it is confirmed using the Schirmer’s test. This is performed using a filter paper strip that has to be positioned under both the lower eyelids of the patient while these are gently closed. The test takes 5 minutes, and after this time has lapsed, the moisture on these strips is evaluated: if it involves less than 10 mm the Schirmer’s test is positive, indicating a condition of reduced or absent tears. Since alacrimia as a first sign of TAS is so recurrent many authors suggest to always start diagnostic workup for TAS whenever it is present\(^2\)\(^,\)\(^14\)\(^,\)\(^15\), while its absence almost rules out the condition.\(^8\) In particular, the study of the adrenal function is mandatory, because even the asymptomatic alterations could precede acute adrenal failure, and thus cortisol secretion should be assessed at once and every two years in this subset of patients.\(^2\) In order to treat this symptom, the patient is administered with artificial tears and lubricants to relief the dryness sensation, using viscous preparations for the more severe forms. If the discomfort is progressive, it could be necessary to use continuous-release ocular inserts or punctual occlusion. The treatment is important as untreated alacrimia may lead to keratopathy, keratoconjunctivitis sicca, corneal melt and ulceration.\(^2\)\(^,\)\(^4\) Thus, an annual ophthalmologic evaluation is recommended.\(^12\) Other findings related to this condition can be
lacrimal gland atrophy, pupillary abnormalities (sluggish or tonic pupils), optic atrophy in adjunction to hypersensitivity to dilute miotics 16–18.

Achalasia

Esophageal achalasia of the cardia is found in almost 75-85% of TAS diagnoses 19–21 although a recent paper from Patt and coworkers reported a higher prevalence of 93% 8. Moreover, follow up studies of TAS patients suggest that the vast majority of affected subjects will develop achalasia, perhaps earlier in those presenting severe hormonal defects 3.

Achalasia is described by two findings: loss of esophageal peristalsis and incomplete relaxation of the lower esophageal sphincter 22. The age of onset of this feature usually ranges from 3 months to 16 years 19,20. As suggested for alacrimia, also in children presenting with achalasia is indicated to investigate adrenal functionality as well as other signs and symptoms of the syndrome 2. The clinical presentation of achalasia in these patients is vomiting, weight loss, difficulty to swallow and chronic coughing 23,24, which could precede the diagnosis of TAS of many years 15,23–27.

The method of diagnosing achalasia is manometry, but also timed barium meal esophagogram is quite sensitive for early diagnosis. Manometry is also used to evaluate the severity of the disease and the choices regarding the treatment 2,28.

There is no consensus on first-line treatment of this condition since non-surgical therapy using pneumatic dilation is short-lasting, although inexpensive and effective, whereas esophagocardiomyotomy is more invasive but with long-term benefits 4,28.

Adrenal Insufficiency

Adrenal insufficiency is another of the most common symptoms which usually develops within 10 years from birth 2,26 and only rarely remain undiagnosed until 50 years 29. As it may lead to severe hypoglycemia and can manifests acutely as hypoglycemic crises and hypotension, it is the leading
cause of death in unrecognized TAS patients. Usually, it is accompanied to skin hyperpigmentation, and its diagnosis is made according to the severity of the disorder. Overt adrenal insufficiency is diagnosed by clinical manifestation, low and high basal level of serum cortisol and plasma ACTH, respectively, and a peak serum cortisol level <18 µg/dL following intravenous (i.v.) injection of 250 µg/m² Synacthen (ACTH test). On the other hand, subclinical adrenal insufficiency is defined as an asymptomatic disease with normal basal serum cortisol levels and sufficient cortisol response to ACTH test (peak cortisol <18 µg/dL, and <7 µg/absolute increase in cortisol levels), but with high basal plasma ACTH level. In patients with conflicting results, insulin-induced hypoglycemia test (ITT) should be considered.

Moreover, it is noteworthy that the evaluation of adrenal functionality in TAS patients should not be limited to the glucocorticoid deficiency. In fact, in studies evaluating the function of the zona reticularis, an impairment, demonstrated by low DHEA-S levels, was found independently from the degree of glucocorticoid deficiency, suggesting a precocious failure of this zone. On the other hand, aldosterone deficiency is much rarer, with only few studies reporting alterations of electrolytes requiring mineral-corticoid supplementation. These different susceptibilities in the adrenal cortex, with a center-to-periphery gradient of damage, are not yet fully explained even if two hypothesis have been made: (i) a reduced production of reactive oxygen species during different hormones production, with less consequent oxidative stress, or (ii) the influence of cortical cell renewal that is known to be centripetal. So, if electrolytes disorders should be always assessed and confirmed with aldosterone and renin dosages in order to rule out the rare occurrence of mineralcorticoid deficiency, the evaluation of DHEA-S could represent, along with ACTH, a useful early assessment to detect precocious/initial adrenal failure.
The replacement therapy is always indicated in patients having a diagnosis of overt glucocorticoid deficiency, although some authors, evaluating the follow up of TAS patients, suggested a mere education to manage a treatment of stressful conditions in subclinical/compensated forms. It is important to maintain a strict follow-up with a first evaluation at 3 months after diagnosis and then 2 times every year. The treatment of choice in these patients is hydrocortisone, at the dosage of 10-15 mg/m² every day, in three administrations. The treatment of mineral-corticoid deficiency using fludrocortisone 0.1 mg/day, should be given only with a sure hormonal diagnosis. Adrenal functionality is recommended to be tested lifelong, as previously indicated, also in the presence of an initial normal result especially in the presence of alacrimia or achalasia.

**Neurological disorders**

TAS is characterized by an inconstant but progressive neurological impairment involving the central, peripheral, and autonomic nervous systems, which is the main prognostic factor of these patients (especially exacerbation of neuropathy and cognitive disorders). The age at onset is variable and is usually late (even if it has been reported that can be the first manifest signs), ranging from 2 to 25 years. The most common neurological manifestations are autonomic dysfunctions involving pupillary muscles and hyperreflexia (with a prevalence up to 65% of affected patients) which underlie an upper motor neuron neuropathy. Other neurological signs and symptoms are postural hypotension, hearth rate instability, sweating, impotence, ataxia, dysarthria, distal motor and sensory neuropathy, other disorders of movements and intellectual disability. Unfortunately, these aspects of the syndrome are hardly treatable and do not respond to glucocorticoid treatment even if physical therapy could help to cope with these alterations. In alternative a new possible approach might be represented by the use of N-acetylcysteine (NAC) as recently reported. Authors showed that NAC is capable of reducing levels of thiobarbituric acid reactive substances
(TBARS), an indicator of increased oxidative stress, in patients with TAS. They thus suggested that the long-term effect of antioxidant treatment should be evaluated to determine the real benefit in terms of precluding degeneration in TAS patients.

Finally, mental retardation is the most common cognitive deficit and, although assumed to probably depend from recurrent hypoglycemia, it is reported also in patients without manifest adrenal insufficiency. Therefore, it might be considered a manifestation of the disease itself. Moreover, similarly to other neurological manifestations of the disease, it seems to be progressive.

Oral disorders and other clinical manifestations

Among the other manifestations of the syndrome, hyposalivation which lead to xerostomia, is an important feature, as it could contribute premature tooth loss, oral infections and to dysphagia. It is confirmed using sialometry and artificial saliva seems to be useful.

Palmoplantar hyperkeratosis is another manifestation found in almost half of the patients and could represent a suggesting diagnostic evidence in patients with TAS.

A peculiar habitus with short stature, long narrow face, thin upper lip and no eyelashes may also be present, as well as osteoporosis, dyslipidemia and long QT syndrome have been described as well.

Molecular Genetics

TAS is caused by mutations in the AAAS gene in most of the studied cases and it is inherited in an autosomal recessive pattern. The gene was first localized to 12q13 and was then further characterized by studies of linkage disequilibrium leading to the identification of its 16 exons and product. The AAAS gene codifies for ALADIN, a 546 aa protein weighting 60 kDa. While the mRNA was found to be ubiquitously expressed in all tissues, the protein ALADIN was found to be
strongly expressed only in the pancreas, adrenal and pituitary gland. A splicing isoform of AAAS, called AAAS-v2, was also reported and detected in brain, liver, kidney, pancreas, thymus, testis and ovary. This isoform excludes the exon 6 in respect to AAAS-v1, the main isoform, and encodes for a 513 aa protein with three WD repeats one less than AAAS-v1.

ALADIN is a nucleoporin that localizes at the nuclear pore complex (NPC) on the cytoplasmatic side and is anchored by the nucleoporin NDC1. A study by Rabut and colleagues (2004) classified ALADIN as a “barely exchangeable” scaffold protein of the NPC with a very low dissociation rate and a high residence rate. ALADIN is part of the WD repeat family of proteins, having four WD repeats, that have been found to be involved in many different functions such as protein-protein interaction, RNA processing, cytoskeleton assembly, control of cell division, signal transduction and apoptosis.

Immunohistochemical analysis showed that mutated or truncated ALADIN localizes to the cytoplasm rather than to the NPC. Indeed, Cronshaw and coworkers found that the essential residue necessary for nuclear pore localizations is located between amino acids 478 and 499. The group also noted that the c.43C>T AAAS mutation in exon 1 produced a protein that was still capable of causing the syndrome despite correctly localizing to the nuclear pore complex. The reason behind the pathogenicity of this apparently anomalous variant was later discovered by Krumbholz et al. which found that the c.43C>T mutation lead to an altered splicing event resulting in the decay of the incorrect mRNA or in a short ALADIN protein improperly localizing to the cytoplasm.

While the exact function of the ALADIN protein remains mostly unclear, attempts have been made to clarify the pathogenetic mechanism of the different mutations reported, seemingly causing impaired nuclear import of DNA repair proteins and the intensification of oxidative stress status in the cell. Hirano and colleagues studying the mutant ALADIN I482S, found that mutated cells had impaired Aprataxin (APTX) and DNA ligase I nuclear import. ALADIN I482S fibroblasts were also shown to be...
more susceptible to oxidative stress which, together with impaired import of DNA repair proteins, caused increased cell death and may explain the progressive nature of the disease. 23.

The oxidative stress characteristic of the disease was further defined by the finding of Storr et al. that ALADIN is important for the nuclear uptake of Ferritin Heavy Chain 1 (FTH1), a protein that has a protective role against oxidative stress 55. Indeed, Kind and coworkers found an increase of 2.7-fold of reactive oxygen species levels in AAAS mutated fibroblast versus healthy ones with an increase in SOD enzymes of 1.2-fold and a slight decrease in Catalase expression by 0.7-fold 56. Further studies confirmed an increase of oxidative stress in H295R human adrenocortical tumor cells and SH-SY5Y human neuroblastoma cells after AAAS knockdown 25. Moreover, AAAS knockdown in the human adrenocortical cell line NCI-H295R1 induces a decreasing biosynthesis of precursor metabolites required for glucocorticoid and androgen production and a significantly impaired nuclear import of DNA ligase 1, aprataxin and ferritin heavy chain 1 35.

ALADIN also interacts with PGRMC2, a protein belonging to the membrane-associated progesterone receptor (MAPR) group, capable, among other roles, to regulate the activity of CYP P450 cytochromes. This interaction, discovered with co-immunoprecipitation experiments by Juhlen and coworkers, could explain the adrenal atrophy encountered in TAS, as altered PGRMC2 localization may impact microsomal CYP P450 which are involved in steroidogenesis activity in adrenal cells 57.

Of interest, it has also been found that ALADIN depletion impair the correct functioning of NuMa in the mitotic spindle formation process by altering the localization of Aurora A, a serine/threonine kinase involved in the regulation of NuMa localization by phosphorylation. This alteration was found to be less damaging than NuMa depletion, consistent with the relatively milder phenotype of TAS. Indeed, depletion of ALADIN causes a reduction but not elimination of the spindle focusing function of NuMa and Aurora A. As depletion of ALADIN is not enough to block cell division, the authors hypothesize
that ALADIN’s role in the regulation of Aurora A simply strengthen the spindle assembly in normal
cells proposing that this role may be more significant in different types of tissue 58. A further insight on
the role of ALADIN concerning cell division has been produced by Juhlen and colleagues, discovering
that depletion of ALADIN in human adrenocortical cells and skin fibroblasts result in an accumulation
of PGRMC1 in the cytosol. The mislocalization of this protein impedes its activity at the level of the
mitotic spindle, thus impairing cell division by loss of stability of K-fibers. The group also found that
PGRMC1 is regulated by Aurora A and PGRMC2 that are seemingly impaired in their function by
alterations of ALADIN 59.

Of note, in the first study to assay the effect of an AAAS mutation in the central nervous system, Bitetto
and coworkers found that the c.464G>A mutation caused a reduction in the AAAS-v1 expression but
an overexpression of AAAS-v2 in the patient’s fibroblast. Consistently, ALADIN presence was
reduced in the patient’s brain, cerebellum and spinal cord but remained normal in fibroblast where the
expression of AAAS-v2 was upregulated 60.

To date, 74 mutations in the AAAS gene causing TAS were reported in the literature; most of them are
nonsense and frameshift, accounting for 56.8% of all mutation types, likely producing a truncated and
non-fully functioning protein. Missense mutations account for 28.4% and splice-site mutations account
for 14.8% (See Figure 1) 3,9,41,61–69,10,70–79,11,80–89,12,90–99,16,100–109,26,110–119,29,120–126,38,39.

Mutations were found throughout the AAAS gene, suggesting no hotspots. However, Patt and
coworkers
found that some of the most recurring mutations exhibit a clustering in certain geographical areas, such
as c.1432C>T and c.787T>C for Europe, c.771delG for China, c.43C>A and c.762delC for India and
the very commonly reported splice-site mutation c.1331+1G>A for Africa and USA8.
Three deletions have also been reported as pathogenetic mechanisms causing TAS. The first is an Alu-mediated rearrangement causing a 3.2 kb deletion implicating the 5’-flanking region, exon 1, intron 1 and exon 2 of the AAAS gene, the second is the g.16166_17813delTGAGGCTGCTG homozygous indel mutation encompassing introns 7 to 10 of the AAAS gene, the third is the recently reported g.53306793_53321761del homozygous deletion of the exon 7 of C12orf10 and all exons of the AAAS gene. Furthermore, a few heterozygous AAAS gene microdeletions implicating also the HOX gene clusters and neighboring genes have been reported causing psychomotor retardation and skeletal abnormalities but not causing TAS symptoms, despite being possible conductors for the syndrome if another disease-causing mutation were to occur.

**Next Generation Sequencing techniques applied to Triple-A Syndrome**

The majority of TAS cases were reported to be due to mutations of the AAAS gene, however a minority of cases (below 10%) presented with no clear underlying genetic cause. Recently, a Whole Exome Sequencing (WES) experiment has been performed by Kohler and colleagues on 13 patients affected by alacrimia, achalasia and intellectual disability but, interestingly, not by adrenal insufficiency, with no mutations in the AAAS gene. The group found mutations in the GMPPA gene, that produces a 420 aa protein called GMPPA (GDP-mannose pyrophosphorylase A). The function of this enzyme is not currently understood but the closest homolog GMPPB mutations are involved in glycosylation defects. The phenotype of these patients did not fully overlap with the TAS and so were diagnosed with AAMR (Alacrimia, Achalasia and Mental Retardation). A novel splice-site variant mutation in the gene GMPPA was also discovered in a WES experiment by Gold and coworkers in two affected sisters from a consanguineous Lebanese family with TAS-like symptoms, but no alteration in the AAAS gene.
Another WES experiment performed by Kohler et al. discovered a novel splice-site mutation in *TRAPP Ci11* in two families with symptomatology overlapping that of TAS and not carrying mutation in *AAAS* and *GMPPA* genes. TRAPP11 is a transport protein and was known to be involved in myopathy\textsuperscript{133}.

It should be then stressed that patients suffering from achalasia and alacrimia with suspected TAS but carrying no mutations in the *AAAS* gene should be prime candidates from WES to hopefully understand more extensively the molecular genetics signature of the Triple-A and TAS-like Syndromes.

**Triple-A Syndrome in-vitro and in-vivo models**

As previously showed, most of the studies featuring models were based on *in vitro* studies of adrenocortical cells and fibroblast cells and helped clarify some aspects of the TAS \textsuperscript{23,25,35,55,56}. A mouse model *Aaas* \textsuperscript{-/-} has also been designed to hopefully recapitulate the disease in a more advanced model. Unfortunately, Huebner and coworkers demonstrated that the phenotype of *Aaas* \textsuperscript{-/-} mice did not recapitulate the human TAS and are characterized by mild abnormal behavior and few neurological deficits. Female *Aaas* \textsuperscript{-/-} mice were also found to be sterile\textsuperscript{134}.

Juhlen and colleagues attempted to study the role of oxidative stress regulation in *Aaas* KO and Aaas KO and heterozygous for superoxide dismutase 2 (*Aaas KO/Sod2 Het mouse*) that should have an increased susceptibility to oxidative stress, to generate a phenotype similar to that of the TAS. Interestingly, while this model failed to recapitulate any of the symptoms typical of the TAS, it showed that *Aaas KO/ Sod2 Het mouse* were able to compensate for the additional oxidative stress by upregulating Nnt which in turns sustains high glutathione (GSH) levels. This compensatory mechanism partly explains why mice ALADIN-deficient lack the TAS syndrome phenotype and resemble WT mice\textsuperscript{135}. 


Conclusive remarks

Given the rarity of the condition and the potentially detrimental adrenal insufficiency that is associated with TAS syndrome, with this review we aim to stress the importance of an early investigation of children presenting with alacrima, achalasia, or other cardinal symptoms of the syndrome.

In fact, TAS is a heterogeneous disease that can have a more complex presentation than the classic triad of ACTH-resistant adrenal insufficiency, alacrimia and achalasia. Esophageal achalasia and adrenal insufficiency are the usual presenting manifestations. Nevertheless, alacrimia is the earliest and most consistent feature (although often overlooked by parents and clinicians) and many other clinical manifestations have been associated to the disease; thus, a more complex and comprehensive approach to this syndrome could facilitate an early diagnosis of the disease. Better awareness of the disease, followed by vigilant observation for the development of adrenal insufficiency, is warranted to improve survival rates.

Different therapeutic options could be adopted for the efficient treatment of the cardinal signs of this syndrome and the efficacy of antioxidant treatment for the management of the progressive neurological degeneration showed in TAS patients is a promising therapeutic option that needs to be confirmed by further studies.

When TAS is suspected, molecular genetic testing offers definite confirmation of diagnosis, early management as well genetic counseling and reproductive options for the family.

Mutations in patients with TAS are distributed through all 16 exons of the gene. No hot-spots are identified in the gene and a comprehensive testing necessitates sequencing of the entire gene and especially intron-exon junction. To date, no clear-cut genotype-phenotype correlation could be deduced from the current literature, confirming the variable interfamilial and intrafamilial clinical presentation of TAS. The reason behind this high clinical heterogeneity is not known but it would be worth to investigate the potential involvement of other genes or mechanism in modulating the different aspects of the pathology. Moreover, some patients with TAS were reported with no mutations in AAAS gene, resulting elective candidates for WES analysis, that should be performed in order to identify new candidate genes and thus improving early diagnosis in all TAS and TAS-like patients.
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