CASE REPORT

Novel Mutations in a Patient with Triple A Syndrome

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Background: Triple A syndrome (Allgrove syndrome), a rare autosomal recessive disorder, is characterized by adrenal insufficiency, achalasia cardia and alacrimia. It is caused by mutations in *AAAS* gene which encodes a protein called ALADIN. **Case characteristics**: 8-year-old boy who presented with hypoglycemic seizures, dysphagia, dry eyes and hyperpigmentation. Investigations confirmed achalasia cardia and adrenal insufficiency. Sequencing of *AAAS* gene revealed two novel mutations in compound heterozygous state (c.1101delG/ c.1310_1311delCT). **Outcome**: Patient was managed with hydrocortisone and artificial tears. **Message**: Sequencing analysis should be done to confirm the diagnosis of clinically suspected Triple A syndrome.

Keywords: *Achalasia cardia, Adrenal insufficiency, Alacrimia, Allgrove syndrome*.

Triple A syndrome is characterised by the triad of adrenal insufficiency, achalasia and alacrimia [1]. In addition a variety of neurological problems affecting the central, peripheral and autonomic nervous system may be present [2]. Triple A syndrome is caused by the mutation in the *AAAS* gene which encodes for the protein ALADIN, a constituent of the nuclear pore complex whose function is not well understood [3,4]. We report a case of triple A syndrome with two novel mutations present in a compound heterozygous state.

CASE REPORT

An 8-year-old boy born to non-consanguineous parents presented to us with generalized tonic clonic seizure that lasted for more than 20 minutes. There was a history of repeated vomiting and progressive dysphagia – more to fluids than to solids – since two years of age. In addition, his parents noted no tear formation while crying since age of two years.

His height (116 cm) and weight (16 kg) were below 3rd centile, and head circumference was 51 cm (between 3rd and 50th centile) with a body mass index of 11.9 kg/m^2. Blood pressure (66/40 mm Hg) was below 5th centile. There was palmoplantar hyperkeratosis with generalized hyperpigmented skin, knuckles and gums. Neurological examination revealed nasal speech and mild intellectual disability. His gait was clumsy and shuffling; pes cavus was present due to peripheral neuropathy. He also complained of photophobia.

Laboratory examination revealed hypoglycemia (blood glucose 25 mg/100mL) Na^+ 138 mEq/L, K^+ 4.3 mEq/L, plasma ACTH 1863 pg/mL and basal cortisol levels <0.20 µg/dL. Decreased tear production was recorded by Schirmer test. Barium swallow test showed a dilation of the esophagus with narrowing of its lower end and tertiary contracture. Magnetic resonance imaging (MRI) abdomen showed normal adrenal glands.

A diagnosis of triple A syndrome was made, and for confirmation the coding sequences of the *AAAS* gene including exon-intron boundaries were amplified from genomic DNA and sequenced. We identified a compound heterozygous *AAAS* mutation consisting of a deletion of G in exon 12 at nucleotide position 1101 resulting in a frame shift at amino acid cysteine 368 as the first affected amino acid, and a premature stop codon at position 48 of the new reading frame (c.1101delG; p.Cys368Alafs*48 or short description p.Cys368fs). On the other allele, we identified a two base pair deletion in exon 14 at nucleotide position 1310-1311 resulting in a frameshift at amino acid proline 437 as the first affected amino acid and a premature stop codon at position 3 of the new reading frame (c.1310_1311delCT; p.Pro437Argfs*3 or short description p.Pro437fs) (***Fig.* 1**). The mother carried the p.Cys368fs mutation in heterozygous state, whereas the father was heterozygous for the p.Pro437fs mutation.

The patient was treated with replacement dose of oral hydrocortisone (15 mg/m^2/day) and topical eye lubricants. On regular follow-up after 20 months, the patient improved and pigmentation decreased significantly.

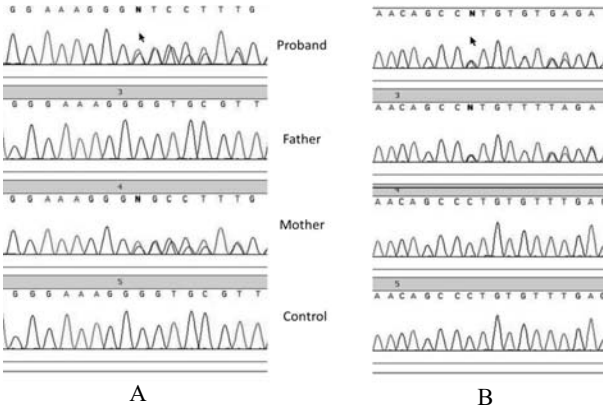

FIG. 1 *Sequence chromatogram of proband, father and mother showing c.1101delG mutation in exon 12 of AAAS gene in proband and mother(A) and c.1310_1311delCT mutation in exon 14 of AAAS gene in proband and father.*

DISCUSSION

In triple A syndrome, alacrimia is usually the first manifestation [5]. Achalasia appears with advancing age in two-thirds of the patients [6]. Adrenal insufficiency normally arises later in life developing gradually over the first decade, but in some cases hypoglycemia and seizures may also occur as presenting symptoms contributing to the diagnosis of the disease. In our case, achalasia appeared at the age of 2 years and adrenal insufficiency, hypoglycemia and seizures appeared at the age of 8 years.

Triple A syndrome is caused by mutation(s) in *AAAS* gene, located on chromosome 12q13 [7]. Around 68 mutations have been reported in *AAAS* gene and most of them produce a truncated protein, although missense and point-mutations have also been described [8]. *AAAS* encodes a protein called ALADIN for alacrimia, achalasia, adrenal insuficiency and neurological disorder [9]. In the present case, two novel mutations were identified in a compound heterozygous state (c.1101delG/ c.1310_1311delCT).

The gene product named ALADIN consists of 546 amino acids, and belongs to the WD-repeat protein families [3]. The function of this protein is not clear yet, it is a protein of the nuclear pore complex (NPC). NPC is critical for communication between the nucleus and the cytoplasm of cells [10]. However, electron microscopic analysis of cells from triple A syndrome patients showed no morphologic abnormalities in NPC, suggesting that mutation in *AAAS* results in a functional rather than a structural abnormality in NPC. No specific genotype-phenotype correlation is found among Triple A syndrome patients.

Alacrimia is diagnosed by Schirmer test while achalasia of the cardia and adrenal insufficiency are best diagnosed by esophageal manometry and ACTH-stimulated cortisol levels, respectively. Alacrimia is treated with artificial tears while achalasia can be treated with either pneumatic dilatation or Heller's myotomy. Adrenal insufficiency is treated with glucocorticoid and if necessary mineralocorticoid replacement. However, currently there is no effective therapy for neurological manifestations.

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