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Case Report Open Access

Novel Mutation in the AAAS Gene in a Severely Affected Triple-A Syndrome Patient

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Abstract

Triple-A syndrome known as Allgroves syndrome classically present with: achalasia, alacrimia and adrenal insufficiency. Ataxia and autonomic dysfunction is additionally described in many cases. We present a case report of a young man of Pakistan origin with achalasia, alacrimia, adrenal insufficiency, ataxia and autonomic dysfunction. Genetic screening identified a novel mutation in the AAAS gene resulting in a homozygous point-mutation

Keywords: Allgrove syndrome; triple-A syndrome; esophageal achalasia; adrenal insufficiency; ataxia

Introduction

The Triple-A or Allgrove syndrome is a rare autosomal recessive syndrome classically represented by the triade of Adrenal insufficiency (Mb. Addisons), Achalasia, Alacrimia and often various degrees of autonomic symptoms and cerebellar ataxia [1,2]. The syndrome is linked to the AAAS gene encoding the protein ALADIN (Alacrimia, Achalasia, Adrenal insufficiency and neurological disorder) which is localized to the nuclear pore complex. Mutations leads to a delocalization of the protein to the cytoplasm, however, its function have not yet been elucidated [3]. The AAAS gene is expressed in neuroendocrine and gastrointestinal structures, the same structures being dysfunctional in the Triple-A syndrome [4]. Due to the recessive inheritance and the rarity of mutations, the syndrome often affects children born in geographically isolated areas or from consanguineous parents. Although variable, the onset of the syndrome is mainly in early childhood. The symptoms have variable expressivity and reduced penetrance and consequently the phenotypic presentations vary depending on the organs affected, which may delay a correct diagnosis. No clear genotype-phenotype correlation is established and patients carrying the same mutation present heterogenic phenotype, severity and age of onset. Therefore, genotype analysis cannot be used to predict future outcome [5].

Case Report

Our case presents a 22 years old man from the region of Lahore, Punjab in Pakistan born at term after an uneventful pregnancy. The parents were first cousins and both healthy. He was asymptomatic until the age of six. At this age, he started to use glasses and artificial tears due to alacrimia. Eight years old, he fell behind in school and complained about fatigue. Objective findings included hyperpigmentation of lips, gums, nails and elbows. Tests verified adrenal insufficiency with isolated cortisol deficiency and treatment with hydrocortisone began. At the same time the patient complained about dysphagia and muscle weakness and was referred to a neurologist and gastroenterologist. Achalasia was identified by barium swallow in 2001 and he had his first dilatation of the cardia as 9 years old.

Because of the three coherent diseases, physicians applied the clinical diagnosis Triple-A Syndrome. Other findings included delay of mental development, hyperreflexia, immature speech and a positive Romberg's sign. Later hyper-nasal voice, dysarthria and intermittently sinus tachycardia were described. MRI of the cerebrum and orbita showed a slightly enlarged optical nerve on the left side. Otherwise the cerebrum and the cerebellum were without significant findings.

To confirm the clinical diagnosis of Triple-A syndrome, we performed a genetic screening of the AAAS gene, identifying a homozygous point mutation: c.43 C>T nucleotide substitution in exon 1, resulting in the replacement of a glutamine with a stop codon, p.Gln15* at the protein level, consistent with the triple-A diagnosis. This is a novel mutation, predicted to cause loss of normal protein function either through protein truncation or nonsense-mediated mRNA decay. In the same position a c.43>A, p.Gln15Lys has previously been reported in a Greek family(Papageorgiou et al. 505-09). We obtained the family history; however, there were no reports of additional cases. The result shows in Figure 1.

Discussion

This case report is characteristic of the complexity of the Triple-A syndrome. The patient was referred to several physicians before the syndrome was diagnosed. Even after his diagnosis, physicians had difficulties linking his autonomic symptoms to the syndrome. He is probably born with alacrimia, but the importance of this finding was not significant until the onset of the other symptoms. What primarily brought him to the pediatrician were symptoms of adrenal insufficiency, which usually present within the first decade of childhood, but with a wider variety of age [6]. The exact percentage who develop adrenal insufficiency is unknown. In a review of nine studies including 52 Triple-A patients, 50 suffered from adrenal insufficiency, 38 from the time of diagnosis. Six were diagnosed later on, suggesting that the penetrance of adrenal insufficiency is relatively high [7-14]. Histology of the adrenal cortex of triple-A patients has shown atrophy of the fasciculate and reticulate zones while the glomerulus zone is often preserved. This is consistent with our case as the patient showed no mineralocorticoid deficiency and was treated only with hydrocortisone [15]. The major complaint of our patient was achalasia. Achalasia is present in approximately 75% of described cases with a wide variety in age, but often with an onset before the age of 16. Compared to children with idiopathic achalasia, triple-A patients often have a severe outcome with failure of the different treatment modalities [16]. Our patient had

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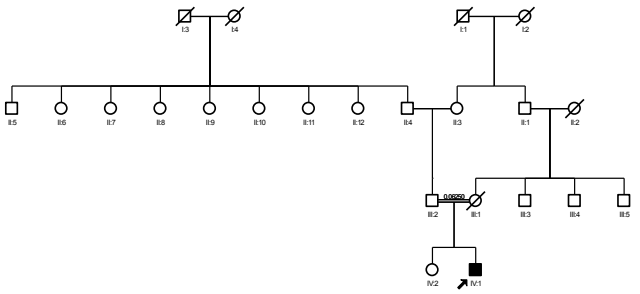

Figure 1: Nonsense-mediated mRNA decay.

dilatation of the cardia and botox injections in the cardia area several times without sufficient effect. Today he still suffer from unsatisfactory weight gaining and dietary troubles, with height 170cm and weight 52 kg, resulting in BMI 18.0. Finally, our patient suffers from dysautonomia. MRI of the cerebrum revealed no significant findings. We found no MRI descriptions of the cerebrum of Triple-A patients in the literature. The neurological symptoms varies with some patients displaying a slowly worsening Amyotrophic Lateral Sclerosis (ALS)-like disorder, other patients suffer from multisystemic neurological disorders with cognitive involvement, cerebellar dysfunction, dysautonomia, ataxia and neuro-ophthalmologic symptoms. Neurological symptoms are often predominant in late onset Triple-A syndrome in adults [17]. Our patient had the clinical diagnosis at the onset of the autonomic symptoms; however he went to both a neurologist and a cardiologist before physicians could link his autonomic symptoms to the syndrome. Most cases in the literature are patients of Arabian, north-African and Iranian origin. A founder mutation was described in several unrelated patients of this origin [18]. Analysis with a likelihood based haplotype approach estimated the age of the mutation to be 1000-1175 years, a time with significant migration to the Arabian Peninsula, which might explain why the Triple-A syndrome is more frequently found in patients with this ethnicity [19,20]. Furthermore, first cousin marriage is common in these cultures, which facilitate the syndrome because of its recessive inheritance. In our case report, the parents were first cousins, both from the region Lahore in Pakistan, an area perhaps influenced of the above-mentioned migrations. Our patient shows the diversity and complexity of the triple-A syndrome. Because of its rarity, it is unknown to many physicians and therefore challenging to manage. The correct diagnosis requires a close correspondence between many departments and accordingly, it is difficult to estimate a precise incidence and prevalence of the syndrome. Both the patient and his father gave their informed consent prior to the making of the case report.

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Conflicts of Interest

The authors have no conflicts of interest

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