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 triad of Adrenal insufficiency (MH. 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 lead 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 before 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 failure of the different treatment modalities [16]. Our patient 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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