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Allgrove syndrome: a report of a unique case characterised by peculiar dental findings resembling those of ectodermal dysplasia

ABSTRACT

Background *Triple A or Allgrove Syndrome (OMIM#231550) is a rare, autosomal recessive genetic disorder in which patients typically suffer from chronic adrenal insufficiency due to resistance to ACTH (Addison's disease), esophageal achalasia, and defective tear formation (alacrima). The syndrome is caused by mutations in the AAAS gene on chromosome 12q13 encoding a 546 aminoacid protein named alacrimia-achalasia-adrenal insufficiency neurologic disorder (ALADIN), a constituent of eukaryotic nuclear pore complexes.*

Case report *We describe a case of Allgrove Syndrome presenting with anhidrosis and peculiar dental features resembling those of Ectodermal Dysplasia (ED).*

Conclusion *Given the clinical findings in this case we suggest the hypothesis that the pathogenetic mechanism in Allgrove syndrome is related to the ED.*

Keywords *Allgrove Syndrome; AAAS gene; Conical shaped teeth; Ectodermal Dysplasia; Enamel hypoplasia; Hypodontia.*

Introduction

Triple A syndrome, also known as Allgrove syndrome, is a rare multisystemic disorder, first described in 1978 and characterised by adrenocorticotropic hormone-resistant adrenal insufficiency, achalasia and alacrima [Allgrove et al., 1978]. In addition, patients often have a variety of neurological symptoms, including amyotrophy of the distal limb muscles, lower cranial nerve weakness resulting in dysarthria and nasal speech, hyperreflexia, ataxia, optic atrophy and rarely sensory impairment such as postural hypotension, impaired cardiovascular reflex, cardiac dysrhythmias, anisokoria and absent or reduced sweating [Gazarian et al., 1995]. Furthermore axonal motor neuropathy with early selective involvement of the ulnar nerve has been found [Grant et al., 1993]. Occasionally, a dermatological involvement is evident such as palmoplantar and punctate hyperkeratosis [Houlden et al., 2002]. Causative mutations have been identified in the AAAS gene on chromosome 12q13 [Weber et al., 1996]. The product of the AAAS gene was identified as tryptophan aspartate-repeat protein called ALADIN, a nucleoporine component of the nuclear pore complex (NPC) [Tullio-Pelet et al., 2000]. AAAS gene is ubiquitously expressed in human tissues, but abundant expression has been observed in the adrenal and pituitary glands, cerebellum, gastrointestinal organs and kidney; the widespread distribution of ALADIN may explain the large number of affected systems and the diversity of symptoms observed in Triple A syndrome [Handschug et al., 2001]. Nucleoporins are involved in transport processes between the nucleus and the cytoplasm. The mutant ALADIN has been shown to mislocalise to the cytoplasm, a condition that results in the failure to import DNA repair proteins (aprataxin and DNA ligase I) and ferritin heavy chains into the nucleus; the resultant hypersensitivity to oxidative stress may trigger cell death in the tissues where ALADIN is widely expressed [Hirano et Al., 2006; Storr et al., 2009]. Apparently, there is a weak genotype-phenotype relationship, which is reflected by the intrafamilial phenotype variability reported [Sandrini et al., 2001].

Here, we report on a case of Allgrove Syndrome presenting esophageal achalasia, alacrimia, adrenal insufficiency, anhidrosis, hypospadia, hyposalivation and peculiar dental findings; in particular enamel hypoplasia, anomalies in number (hypodontia) and shape (knife-edge and conical) of the teeth. The latter features resemble those of Ectodermal Dysplasia (ED).

Case report

The affected propositus is a male subject who was 12 years old at the time of diagnosis of Triple A Syndrome. He is the first child born to healthy unrelated Caucasian parents. A history of the genetic disorders was not reported in his family. He was born by caesarean section delivery at the thirtieth week of pregnancy, weighed 1.00 kg and immediately required surfactant replacement through intubation to deal respiratory distress. He showed bilateral cryptorchidism with inguinal location of testes, mid-shaft hypospadias while the karyotype result was 46,XY. At 3 years of age, surgery sec Bracka for hypospadias and cryptorchidism was performed.

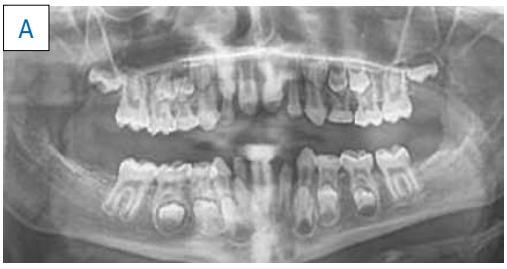
He presented progressive dysphagia, vomiting and feeding difficulties resulting in weight loss complicated by aspiration pneumonia. Barium swallow studies showed a dilated esophagus with "bird's-beak" tapering of the distal esophagus, and which pointed to suspected achalasia. The diagnosis was confirmed by esophageal manometry. At 7 months of age he underwent laparoscopic Heller myotomy and Dor fundoplication with resolution of the symptoms of achalasia at the 1 year follow-up.

He started walking at 15 months, but his balance did not improve in the following years. Pes planus and left Achillean retraction were documented at the age of 2.3 years, and he frequently fell while walking. The orthopaedic specialists prescribed splints for his feet but no improvement in his balance was evident. The neurologic evaluation revealed wasting and weakness of the calves. His plantar reflexes were equivocal but no sensory defect was present. Alacrimia was confirmed with Schimer test at the age of 2 years and his mother reported that he always "cried without tears". He also displayed reduced sweating as demonstrated by starch iodine test. At the age of 9 years, the time of our first observation, the facial appearance was characterised by hypertelorism, prominent ears, malar hypoplasia and prognathism, with dysarthria and nasal speech. He had no hyperpigmentation or hyperkeratosis of the skin (Fig. 1). At this age, an accurate inspection of the mouth revealed caries on the occlusal surface of teeth 54 and 75, abnormal knife edge shape of teeth 11, 21, 32 and 42, while teeth 71 and 81 had a conical appearance. These dental features are typical of the ED.

A diffuse yellow-orange discoloration on most of the teeth surfaces was detected (Fig. 3), and a yellow-brownish discoloration was seen in teeth 71 and 81 (Fig. 3a); enamel hypoplasia of the vestibular palatal/lingual surfaces of the 8 primary molars present in the mouth was detected. Erosion, probably due to recurrent vomiting and gastroesophageal reflux, was common in all erupted teeth, both primary and permanent. We could not assess the level of enamel hypoplasia because the diagnosis is histological.

The orthopantomogram defined the severity of hypodontia and the agenesis of 8 permanent teeth, 31, 41, 37, 47, 18, 28, 38, 48 (Fig.2a); a teleradiography (Fig. 2b) showed a skeletal Class III, which was clinically evident and defined by prognathism.

FIG. 1 Facial dysmorfism caracterised by hypertelorism, prominent ears, malar hypoplasia and prognathism.



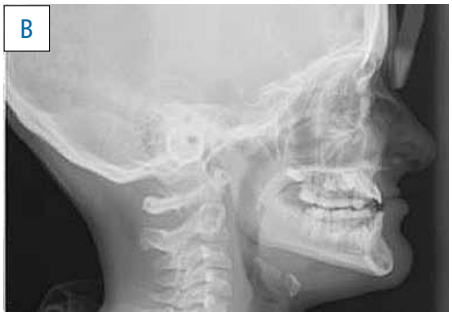


FIG. 2 Orthopantomography shows agenesis of teeth 31, 41, 37, 47, 18, 28, 38, 48 (A). The teleradiography shows a skeletal Class III with mandibular protrusion (B).

Laboratory investigation revealed ACTH-resistant adrenocortical insufficiency with high plasma levels of ACTH (852pg/ml), low levels of cortisol (1.5 ng/ml) and low serum dehydroepiandrostenedione-sulfate (DHEA-S 30 mcg/dl) and a normal range of aldosterone, plasma renin activity (PRA) was measured. Treatment with hydrocortisone was commenced. The clinical diagnosis of Triple A syndrome was confirmed by molecular genetic analysis of the AAAS gene: the patient is compound homozygous for a C>T transition in exon 11 at nucleic acid position 1024 (c.1024C>T), resulting in a change of the arginine at the amino acid position 342 into a stop codon (p.Arg342X, p.R342X).

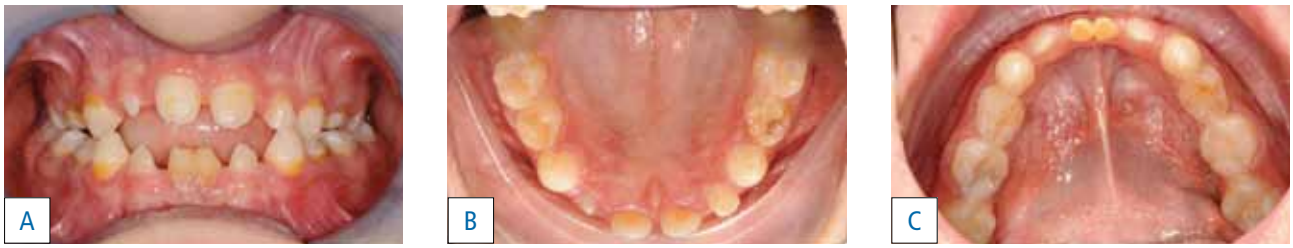


FIG. 3 Intraoral view of the mouth. Bilateral crossbite, knife edge shape of teeth 11, 12, 32 and 42, knife conical shape of teeth 71 and 81 (A). Intraoral occlusal view of the upper and lower jaw showing a mixed dentition compatible with the age of the patient and erosion of the occlusal surfaces. Decays on teeth 54 (B) and 75 (C) are visible.

Discussion

We report on a 12-year-old young boy with Allgrove syndrome who, in addition to the original three 'A's (alacrimia, achalasia and adrenal insufficiency), presented amyotrophy and anhidrosis [Mathew et al., 2013]. Anhidrosis was diagnosed with provocative starch-iodine sweat test, which showed a marked reduction in activated sweat gland density. We known that all ectodermal dysplasia subjects with anhidrosis present reduced number of sweat glands but reason of altered sweating in patients with Allgrove Syndrome revealed dysautonomic disorder, such as abnormal innervation of sweat glands. In addition, our patient also presented hypospadia, hypodontia, misshapen teeth, aand skeletal Class III or prognathism (Fig. 1a, 2b), and hyposalivation. These dental abnormalities are characteristic features of ectodermal dysplasia. The most common oral features in Allgrove syndrome reported in the literature are xerostomia [Li et al., 2014; Dumic et al., 2012; Vallet et al., 2012; Vucicevic-Boras et al., 2003], malar hypoplasia, prognathism in concomitance with normal permanent teeth [Bizzarri et al., 2013], fissured tongue [Li et al., 2014], furrowed tongue with fasciculation [Nakamura et al., 2010], periodontal disease [Chu et al., 1996]; premature loss of teeth with unspecified origin has been reported [Palka et al., 2010], loss of teeth due to caries and periodontal disease along with hyperpigmentation of the lips and in the oral cavity [Chu et al., 1996]. Edentulism, of unknown origin, has been reported in two 12-years-old siblings [Razavi et al., 2010]. A combination of xerostomia, caries, periodontal disease, and premature teeth loss has been described by Li et al in three out of six patients [2014]. Compared to the previous reports, our patient had hypodontia, enamel hypoplasia and misshapen teeth (knife edge in lateral lower incisors and conical shape in central primary lower incisors).

Conclusion

To the best of our knowledge this is the first report describing the association of hypodontia, enamel hypoplasia and misshapen teeth, anhidrosis with the classic findings of the triple A syndrome, i.e. alacrimia, achalasia and adrenocortical insufficiency, designated further as Four A syndrome due to the presence of amyotrophy. The syndromic complex occurring in our case would suggest that a pathogenetic mechanism similar to ED is operating in Allgrove syndrome.

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