ORAL MANIFESTATIONS OF TRIPLE A (ALLGROVE) SYNDROME IN SIBLINGS
Mehdy Davarmanesh, Maryam Zahed Zahedani, Sahaab Shahrzad

ABSTRACT

Triple A syndrome is a rare autosomal recessive disorder. The major manifestations of the involved patients are adrenal insufficiency, achalasia and alacrimia, long narrow faces, high arched palate, oral pigmentation and fissured or atrophic tongue. Xerostomia is also recognized as a consistent oral finding in the patients. Aside from challenges in management of xerostomia and its complications, the association of these conditions in childhood would be of great clinical importance in diagnosis of a hereditary syndrome which encompasses noticeable systemic features. This paper reports the clinical features, differential diagnosis Triple A syndrome in siblings.

Keywords: Allgrove syndrome; oral mucosal pigmentation; triple A syndrome; xerostomia.

Introduction

Triple A or Allgrove syndrome (OMIM 231550) was first described by Allgrove et al. in two pairs of unrelated siblings. The triple A stands for the three most prominent features of the syndrome, alacrimia (absence of tears), achalasia (esophageal motility disorder) and adrenocorticotropic hormone (ACTH)-resistant adrenal insufficiency. The incidence of this rare multisystemic disorder is unknown. Until now, about 200 patients have been reported throughout the world and some of these cases are not genetically confirmed. This disease gene was localized at 12q13 in 1996, which was mutant in individuals affected by this syndrome. This gene, called the AAAS gene (achalasia-addisonian-alacrimia syndrome), has an autosomal recessive inheritance and codes the ALADIN protein. Alacrimia Achlasia Adrenal insufficiency Neurologic disorder protien (ALADIN).

New studies have shown that this protein is involved in the nuclear translocation of ferritin heavy chain protein (FTH1). Besides its iron-storage role, FTH1 is also present in the nucleus and acts as a DNA protector. ALADIN deficiency results in impaired FTH1 nuclear uptake, resulting in more susceptibility of cells to oxidative damage. The central nervous system and the adrenal cortex are particularly vulnerable to oxidative stress. There have been various reports of this syndrome in Iranian families. It is suggested that different ethnic groups develop a mutation database of their own and apply it in prenatal diagnosis. Throughout the years other features such as neurologic disturbances have been related to this syndrome and thus the name 4A syndrome has been introduced. The orofacial abnormalities of Allgrove patients reported in the literature include: long narrow dysmorphic faces, long philtrum, down-turned mouth with thin upper lip, cleft palate, incompletely developed fungiform papillae of the tongue, mandibular malocclusion, relaxed speech musculature, movable soft palate, high gothic hard palate, cross bite, macroglossia, fissured tongue, atrophic tongue and hyperpigmentation of the buccal mucosa, gums, lips and perioral area. A nearly complete loss of secondary dentition due to an increased rate of dental caries and periodontitis was first noticed in 1998 by Clark et al. Raza et al observed premature loss of permanent teeth in two related families presenting this syndrome. In 2000 Dumic et al. reported the Xerostomia as a newly recognized finding of triple A syndrome and performed sialometry on 5 patients presenting this syndrome of whom all had oral dryness. Thereafter dry mouth has been reported by others as a feature of this syndrome. Here we describe the oral manifestations of two siblings affected by this syndrome from a consanguineous marriage. The coexistence of reduced saliva and tear secretions and oral mucosal pigmentation seems to be of great implication in the possibly earlier recognition of the syndrome and a better patient management.

Case Reports

A 21 year old female patient diagnosed with triple A syndrome was referred to the Department of Oral Medicine, School of Dentistry, Shiraz, Iran, with the chief complaint of oral dryness and extensive decays in teeth. Triple A syndrome was diagnosed at six years of age when she developed diffuse cutaneous hyperpigmentations accompanied with severe hypoglycemic and hypotensive episodes. Genetic analysis ordered at that time detected a mutation on exon 1 of the AAAS gene (125C -> A). There was no family history of the disease and the parents were related. All the family members were genetically evaluated and the younger brother (patient 2 ) with three years of age (presently 18 years old) was also diagnosed as Allgrove syndrome. Both patients were placed on once daily 5 mg prednisolone thereafter. One year ago, esophageal dilatation (ballooning dilatation) was performed for patient 1, because of difficulty in swallowing. Patient 2 had no problems...
with swallowing. Upon assessment of their medical records no neurological abnormalities had been diagnosed for both. However Patient 1 had shown generalized cutaneous hyperpigmentations of Addisonian character mostly in sun exposed skin surfaces while patient 2 had no signs of pigmentation. At the presentation to the oral medicine department, careful extraoral and intraoral examinations were performed. Bitewing radiographies were taken for the evaluation of interdental caries and bone levels. The periodontal status of the patients were also examined by a periodontal probe. For assessment of the patients’ saliva secretion, whole salivary flow rate was measured in both resting and stimulated states in accordance with the method of Navazesh et al.16 Tear secretion was measured by Schirmer’s test according to the report of Savini et al,17 using Schirmer’s tear test strips (OphStrip, Ophtechnics Inc, Carson, USA). The measured salivary secretions were expressed as gram/minute and for tear secretion as a length of the wet fraction in millimeters per total length of the strip for the specified duration.

Careful extra- and intra oral examinations showed no grossly visible abnormalities in both patients regarding morphologic features of face, lips, palate and tongue. The patients had no abnormal periodontal findings. On dental examination, patient 1 had extracted two permanent molar teeth due to severe caries. Four teeth had amalgam fillings; five had deep interproximal caries on radiographic examination; one had deep caries with a periapical radiolucency and two teeth had cervical caries. Patient 2 had extracted all four first premolar teeth for orthodontic treatment. Nine teeth had amalgam fillings. Root canal therapy had been performed for one. Caries of cervical area was detected on one tooth. Careful inspection of the oral mucosal surfaces in patient 1 revealed diffuse light-brownish pigmentation on lateral borders of the tongue and also multiple well-defined macules on both sides of the posterior buccal mucosa (Figure 1, 2). No pigmented sites in the oral mucosa were found in patient 2. The results of the sialometry and Schirmer’s test are presented in table 1. Both patients were considered Xerostomic according to Navazesh et al.16 The intraoral findings observed in our patients were Xerostomia, high rate of dental caries and mucosal pigmentation. The well known major causes of oral dryness are the use of various medications, irradiation of the head and neck, and systemic diseases such as Sjogren syndrome and familial dysautonomia.14 When Dumic et al. introduced the Xerostomia as a manifestation of triple A syndrome, they also observed atrophic and erythematous mucosa, angular cheilitis, glossitis, fissured tongue, candidiasis and tooth decay in their patients.14 In 2003, oral dryness was reported as a presentation of Allgrove patients however other findings as dense and mucous saliva, fissured tongue and extremely carious teeth were also mentioned in the reported patients.15 In our cases oral dryness and dental caries were similarly found but no sign of candidal infections were seen. This could partly be due to a better level of oral hygiene observed in these patients. In 2006 Onat et al. reported two patients with allgrove syndrome who presented by having 5 of the 6 diagnostic criteria for Sjogren syndrome.15 Only the salivary gland biopsies of these patients, the gold standard for diagnosis of Sjogren, were negative. So they concluded that in patients with ocular dryness, xerostomia and positive anti-Ro and anti-La or anti-nuclear antibodies (ANA), salivary gland biopsy is strongly needed, because it prevents misdiagnosis in triple A patients.15 Since both our patients had genetically been studied and confirmed to have the syndrome, we did not perform the biopsy of labial minor salivary glands.

Oral dryness in pediatric patients can be due to developmental anomalies of the salivary glands such as agenesis, aplasia and hypoplasia of the major salivary glands alone or in combination with syndromes like ectodermal dysplasia. Also acute infections, chemotherapy and radiotherapy of the head and neck can cause xerostomia. Other differential diagnoses are rare during childhood, such as gastrointestinal diseases, diabetes insipidus, kidney diseases, malnutrition syndrome, high

<table>
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<tr>
<th>Patients</th>
<th>Tear flow</th>
<th>Salivary flow</th>
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<tbody>
<tr>
<td></td>
<td>Unstimulated (grams/minute)</td>
<td>Stimulated (g/minute)</td>
</tr>
<tr>
<td>Patient 1</td>
<td>&lt; 2 millimeters*</td>
<td>0.07 g/minute**</td>
</tr>
<tr>
<td>Patient 2</td>
<td>&lt; 2 millimeters*</td>
<td>0.09 g/minute**</td>
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Table 1: Sialometry and Schirmer’s test results of the patients  *Low tear secretion as the measured values were far less than 8.1-33.1 as normal reference range without anesthesia.17  **Low salivary secretion, as the results were < 0.1 g/minute for unstimulated and ≤ 0.7 g/minute for stimulated whole saliva measurements.14
fever and dehydration. Thus as suggested elsewhere, possible detection of young patients with dry mouth or its consequences in the field of dentistry and referring them to appropriate medical professionals for further evaluation, would be of benefit for the earlier diagnosis of Allgrove syndrome.11,13

Dry mouth has also been reported in late-onset triple A syndrome.2,11 This means that in unknown cases of late-onset forms of the syndrome where the manifestations of the neurologic dysfunction may predominate over the classic findings, the patients’ dry mouths and its resulting sequelae would be of help for possible detection of the undiscovered cases of the syndrome. In another report of adult onset triple A, atrophic tongue was observed and the tongue was described as “furrowed with fasciculation”.11 The tongues of our patients were normal in size and shape which besides the lack of other neurological findings place them more in the early onset category of triple A syndrome. Extremely carious teeth are another finding we observed similar to other reports.7,8,13-15

Dry mouth can lead to high rates of dental decay and periodontal problems. In one report, loss of permanent teeth was seen in the absence of dental caries.7 This can be related to severe forms of periodontal disease seen in patients presenting this syndrome.8 The fibroblasts of the Allgrove patients have been stated to be more susceptible to oxidative damage, accounting for susceptibility of the patients to severe periodontal disease.5 The patients we reported had no signs of periodontal problems. But since the other characteristic features of the syndrome are believed to potentially progress through the years5 future periodontal recall appointments, seems reasonable for these patients. Pigmentations of skin as a relatively consistent feature in many reports of the syndrome. Pigmentations of the perioral areas, gingiva, lips and buccal mucosa have also been reported.8,12

The main causes of diffuse bilateral pigmentation of the oral mucosa are physiologic pigментations, Peutz-Jeghers and other familial hamartoma syndromes, Addison’s disease, hematologic disorders, drug induced and heavy metal pigmentation.7,17 In Addison’s disease, deficient production of cortisol results in increased production of adrenocorticotropic hormone (ACTH). This is the cause of diffuse dark pigmentations of the skin and oral mucosa.8 This can also be observed in Triple A syndrome due to adrenocorticotropic hormone (ACTH)-resistant adrenal insufficiency. In one of our patients the buccal mucosa and lateral borders of tongue were the intraoral sites where melanotic pigmentation had developed. In the Addison’s disease, the oral manifestations including diffuse or patchy brown pigmentation of melanin origin are often stated to precede the cutaneous hyperpigmentation, however as seems expectable if such phenomenon be the case for triple A syndrome, such oral finding would be of benefit in the earlier detection of the syndrome only if the patients be of a naturally white complexion and so, no commonly-encountered reasons like physiologic pigmentation be considered as a likely cause for the mucosal pigmentation. Certainly, in reports of newly-diagnosed patients in future, more careful observation of the possible intraoral findings i.e., the mucosal pigmentation and mouth dryness or its sequelae will give a better estimate on potential contribution of such features on the earlier detection of patients having the classic syndrome. But it is the first time that a patient’s tongue was found to manifest a pigmented site in this syndrome.

Among the professionals of health care disciplines encountered with patients of this syndrome, dentists can exert a dual contribution i.e., firstly assistance in possible detection of the syndrome by facing the patient’s dental treatment needs and assessment of the relevant intraoral complaints and secondly the management of the complications associated with a poor salivary flow and or periodontitis and tooth loss in patients of the either age groups. Furthermore the poorly-controlled patients can pose a definite challenge for dentists within and even after dental treatments because of ongoing hypoglycemic episode or adrenal crisis. Here two cases of allgrove syndrome have been reported to emphasize the need for referring the involved patients to a dentist for evaluation of caries and periodontal disease. Periodic fluoride therapy, professional oral care, saliva substitutes and oral hygiene instructions must be ordered for prevention of further damage to teeth and periodontal tissues. There have been reports of patients with Xerostomia diagnosed as Sjogren syndrome or Achalasia Sicca, which could be true cases of triple A syndrome but without manifesting adrenal insufficiency at the time of diagnosis.19,20 Also adrenal insufficiency without dominant symptoms can be misdiagnosed as muscle weakness.7

**Conclusion**

In conclusion it is advised that all patients with oral dryness and pigmentations be referred for hormonal tests and medical evaluation in looking for more signs of Allgrove syndrome i.e. achalasia, alacrimia and adrenal dysfunction.

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