Three Cases in Pediatric Neuroradiology: Athabascan Brainstem Dysgenesis Syndrome, Aicardi Goutières Syndrome, and Aplasia of the Parotid Glands

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Dedication/Acknowledgements

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A Presumptive Case of a Rare HOXA1 Mutation Syndrome

Abstract

Summary: The human HOXA1 mutation syndromes commonly present with abnormalities of the inner ear and internal carotid arteries. Previous cases describe varying degrees of hypoplasia or aplasia of the affected structures, often with asymmetrical involvement. We present imaging findings documenting complete absence of the internal carotid arteries bilaterally with bilateral Michel aplasia of the inner ear, which, to our knowledge, has not been previously reported. Based on the number of cases identified and birth rates within studied populations, we estimated the incidence of ABDS at 0.5-1:1000 live births on the White River Apache Reservation and 1:3000 live births in the Navajo population. If accurate, this suggests a carrier frequency similar to that for cystic fibrosis in Caucasian populations. ABDS may represent a significantly underrecognized disorder among Athabaskan Native Americans, raising questions of the possible benefit of genetic counseling for affected families. However, cultural considerations in this population bring into question the possible conflict between counseling based on gene theory and traditional beliefs.

Introduction

Two congenital syndromes with similar features, Bosley-Salih-Alorainy syndrome (BSAS) and Athabaskan brainstem dysgenesis syndrome (ABDS), are recessive disorders linked to loss of function mutations of the HOXA1 gene (OMIM #601536). BSAS has been documented in consanguineous marriages in Saudi Arabian and Turkish families [1-3]. ABDS has been described in Native Americans of Athabaskan (primarily Navajo and Apache) descent [3-5].

HOXA1 mutation syndromes are associated with a number of abnormalities which vary remarkably in penetrance and severity. The most common manifestations include horizontal gaze abnormalities, deafness, internal carotid artery (ICA) malformations, and developmental delays. Congenital cardiac defects, central hypoventilation, facial paresis, swallowing dysfunction, and vocal cord paresis are variably seen [1-5].

We present a presumptive case of the rare ABDS HOXA1 mutation syndrome in a two-year-old Navajo girl.

Case Report

A two-year-old female patient of Navajo descent was assessed for developmental delay. The child was unable to speak or walk, and had failed newborn hearing screens. Brainstem auditory evoked response testing confirmed bilateral sensorineural deafness. She also exhibited impairment of horizontal eye movements and facial diplegia with fasciculations.

MRI of the brain demonstrated absent ICA flow voids and complete absence of the bilateral inner ear structures and internal auditory canals. The 6^{th}-8^{th} cranial nerves could not be identified (Fig 1). MRA of the head confirmed bilateral absence of the ICA with markedly enlarged vertebral and basilar arteries supplying blood flow to the anterior and posterior circulations via an intact circle of Willis (Fig 2).

Based on findings of Michel anomaly, ICA aplasia, horizontal gaze abnormalities and developmental delay in a Navajo child, the presumptive diagnosis of the HOXA1 mutation syndrome ABDS was made.

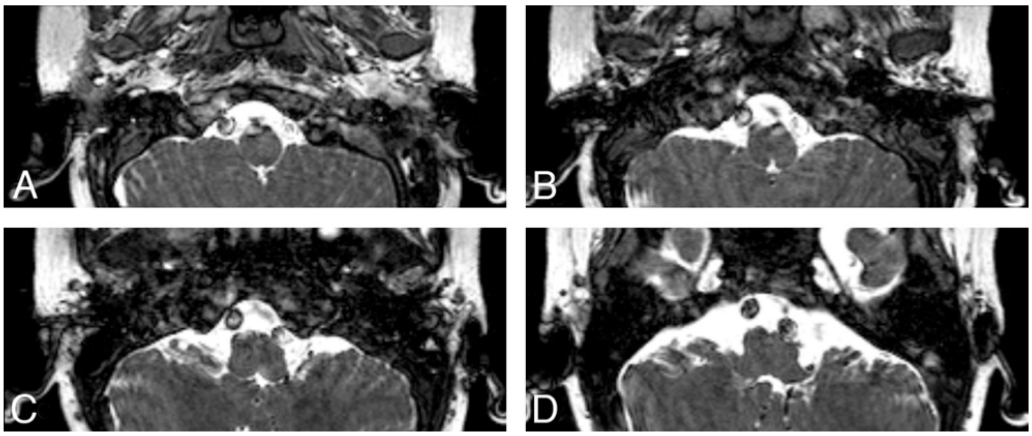

Fig 1. Balanced fast-field echo axial T2 images show complete lack of inner ear structures and internal auditory canals bilaterally.

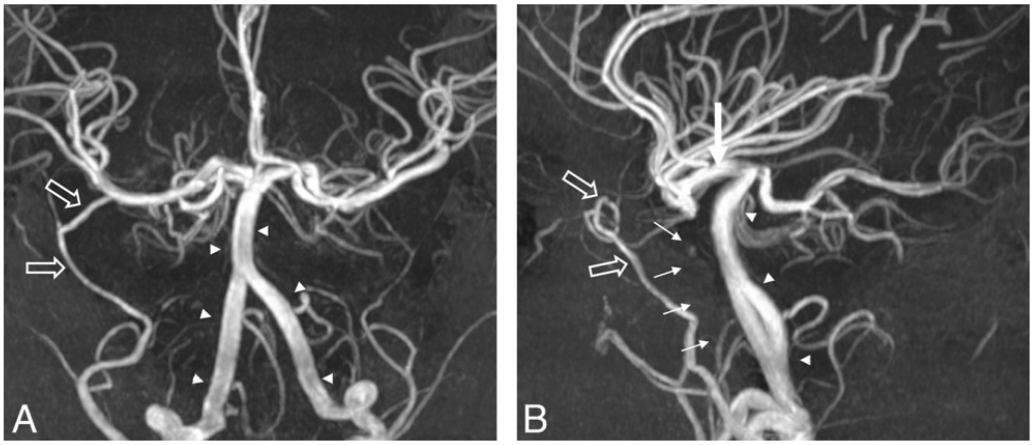

Fig 2. 3D time-of-flight maximum-intensity-projection images in anteroposterior and lateral projections demonstrate complete absence of the bilateral ICAs (small arrows). The vertebrobasilar system is enlarged (arrowheads) and supplies flow to the bilateral anterior cerebral arteries and middle cerebral arteries via enlarged posterior communicating arteries (large arrow). The right middle meningeal artery is enlarged (open arrows).

Discussion

The Navajo are one of several Native American tribes of Athabaskan descent. Recessive genetic disorders occur with increased frequency in Athabaskan tribes, likely due to genetic bottlenecks in the 1800's caused by conflicts with the United States Army [5,6]. In 1996 and 1997, Friedman et al. presented ten cases of ABDS, a congenital syndrome in Athabaskan children featuring horizontal gaze abnormalities, deafness, developmental delay, and central hypoventilation. Variably present features included facial paresis, swallowing dysfunction, vocal cord paresis, seizures, and congenital cardiac anomalies. MRA in three ABDS cases revealed two children with unilateral hypoplasia or aplasia of the ICA. To our knowledge, these thirteen cases are the only previously published cases of ABDS [3-5].

Based on the number of cases identified and birth rates within studied populations, Erickson et al. and Holve et al. estimated the incidence of ABDS at 0.5-1:1000 live births on the White River Apache Reservation and 1:3000 live births in the Navajo population [5,6]. If accurate, this suggests a carrier frequency similar to that for cystic fibrosis in

Caucasian populations. ABDS may represent a significantly underrecognized disorder among Athabaskan Native Americans, raising questions of the possible benefit of genetic counseling for affected families.

In 2005 Tischfield et al. observed a syndrome very similar to ABDS in consanguineous Saudi Arabian and Turkish families. This syndrome, BSAS, has been described in sixteen children. As in ABDS, horizontal gaze abnormalities, deafness, and developmental delay were common findings. Thirteen of the BSAS children had neuroimaging studies, the majority of which exhibited ICA hypoplasia or aplasia. The only major feature of ABDS not found in BSAS patients was central hypoventilation [1-3].

Tischfield et al. and Bosley et al. identified homozygousity for a mutation to the HOXA1 gene in all patients with BSAS (175-176insG, 185delG, or 84C→G). Eight ABDS children, including three new cases, were subsequently studied for HOXA1 mutations. All eight carried a homozygous 76C→T mutation, which results in truncation of the normal 335 amino acid sequence to just 25 residues [1-3].

HOX genes play an important role in determining cell identity along the anteroposterior axis of the embryo. The genes code for transcription factors that interact in a complex manner with a number of other signals to induce tissue differentiation. Different HOX genes are expressed in overlapping temporal patterns and spatial regions along the cranial-caudal axis. HOXA1 is the first of the HOX genes expressed in humans, and is found in the most cephalad distribution. Two HOXA1-/- mouse models exhibit phenotypes similar to the human HOXA1 syndromes, with the exception that cerebrovascular malformations were not documented in mice [1]. Thalidomide exposure between 20 and 24 days gestation also causes anomalies resembling the HOXA1 mutation syndromes [2]. Later exposure to thalidomide and mutations of HOX genes that are expressed later and more caudally both disrupt development of the extremities [1]. These similarities suggest that the teratogenic effects of thalidomide may represent a disruption of the complex HOX signaling cascade [2].

Horizontal gaze palsies and other cranial nerve (CN) dysfunctions were commonly identified in HOXA1 mutation syndrome patients.

Horizontal gaze dysfunction was the single most consistently identified abnormality in these patients, ranging from total horizontal gaze palsy to normal ocular motility in a few patients [3]. HOXA1-/- mice also exhibit horizontal gaze palsies with absence of the 6th CN [2]. Dysfunctions of CN7-10 were variably seen in ABDS and BSAS patients. Facial paresis and deafness were common, while swallowing dysfunction and vocal cord paresis were less often documented [3]. Our patient presented with intact vertical but restricted horizontal gaze, facial diplegia and fasciculations, and sensorineural deafness. CN 6-8 could not be identified on MRI, and are likely severely hypoplastic or absent.

Bilateral deafness was identified in the vast majority of individuals with HOXA1 mutation syndromes, and in all reported cases of ABDS [1-5]. Inner ear structures normally begin development in the third week of gestation. In HOXA1 mutation syndrome patients, genesis of the structures seems to be commonly disrupted between three and seven weeks resulting in a spectrum of malformations. Imaging findings of the temporal bone have not been previously described in ABDS, but have been reported for most BSAS patients. Inner ear malformations

ranged from complete agenesis, or Michel anomaly, to relatively minor cochlear hypoplasia. A few BSAS patients were found to have normal inner ear structures and hearing. In the most striking malformations, unilateral Michel anomaly was identified with common cavity deformity present contralaterally [3]. The present case demonstrates the first known report of bilateral Michel anomaly in a HOXA1 mutation syndrome patient.

Cerebrovascular anomalies, although not seen in mouse models, were identified in well over half of the appropriately studied HOXA1 mutation syndrome patients. Unilateral hypoplasia or aplasia of the ICA was most commonly seen, with bilateral ICA aplasia identified in one BSAS patient [3]. Collateral vasculature may fully compensate for ICA aplasia, but patients may be predisposed to aneurysm formation and future cerebrovascular injuries [7]. MRI and MRA studies of our patient revealed bilateral ICA aplasia with markedly enlarged vertebral and basilar arteries supplying the anterior and middle cerebral vascular territories. To our knowledge, Figures 1 and 2 represent the first published neuroimaging studies in a case of ABDS,

and the first evidence of an ABDS patient with complete bilateral ICA aplasia.

Central hypoventilation is the only major feature which significantly differed between the two HOXA1 mutation syndromes. No BSAS patient was diagnosed with central hypoventilation, while all thirteen previously published cases of ABDS indicated that supplemental oxygen or mechanical ventilation were required [3,5]. In all patients hypoventilation was more severe during sleep, and in the least affected children supplemental oxygen was only required at night [5]. As polysomnography was not conducted on the current patient, it is not possible to rule out mild central hypoventilation during sleep. However, pulse oximetry on room air was normal.

The present case exhibits the most extreme manifestations of ICA and inner ear abnormalities seen in ABDS with complete bilateral aplasia of both. However, unlike every previously reported case of ABDS, she has no documented central hypoventilation. Considering the small number of patients previously studied, we suggest that phenotypic variability is not yet fully appreciated in ABDS. The frequency of the

disorder is also unclear, but preliminary estimates indicate that it could be significantly underrecognized among Athabaskan Native Americans. We believe that identification of any feature of the syndrome in a Native American child should prompt MR or CT evaluation for related abnormalities that would suggest the diagnosis of ABDS.

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Case Report:

Aicardi Goutières syndrome, a heritable mimic of congenital infection

Abstract

Aicardi Goutières syndrome (AGS) is a rare genetic cause of neonatal and early infantile encephalopathy characterized by calcifications of the basal ganglia and white matter, leukodystrophic changes, cerebrospinal fluid (CSF) lymphocytosis, and a high level of CSF interferon (INF)-α. Awareness of this entity is clinically important to prevent misdiagnosis as the sequelae of congenital infection or leukoencephalopathy of unknown etiology. Neuroimaging is essential for diagnosis of AGS.

Introduction

Aicardi and Goutières first reported a familial syndrome of early-onset encephalopathy in 1984. AGS is most commonly inherited via a recessive pattern, but a few cases of *de novo* dominant mutations have been documented. Recently, molecular genetics studies have identified five distinct mutations responsible for the majority of cases[1]. The age of onset, severity of symptoms, and rapidity of progression of AGS are somewhat variable, even within sibships. Because of this variability, the recent advent of definitive genetic testing for AGS, and the high potential for misdiagnosis, the natural history of this disorder is not yet fully understood.

Infants typically present within the first months of life with irritability, sterile pyrexias, slowing of head growth, a characteristic high-pitched cry, and developmental regression. Many also have seizures, dystonia, cutaneous lesions of the fingers, toes, and ears, or hepatosplenomegaly. CSF studies reveal leukocytosis, elevated IFN-α, and high concentrations of neopterin (an indicator of IFN mediated activation of macrophages). In contrast to patients with congenital

infections, AGS patients do not typically have cataracts or chorioretinitis, and present with normal hearing.

Neuroimaging is essential in diagnosing AGS. Cardinal findings include: calcifications of the bilateral basal ganglia and cerebellar dentate nuclei extending into the white matter, leukodystrophy, and generalized cerebral atrophy. Most evident on CT, calcifications vary from punctate to massive, but the extent of calcification does not seem to correlate with severity of symptoms. Some reports indicate that calcification may be absent very early in the course of disease. White matter abnormalities are most clearly identified on T2-weighted MRI as hyperintense signal, particularly in a periventricular distribution[2]. In severe cases temporal cystic lesions can be seen[3].

It is generally accepted that after an initial subacute phase lasting a few months, there is no further progression of the disease. CSF findings normalize, neuroimaging findings are stable, and there is no further regression[2]. However, as a result of the initial phase, most infants are severely impaired and many do not survive early childhood[4].

Case Report

This female patient was the second child of a nonconsanguineous couple with one healthy daughter. She was the product of a term pregnancy and uncomplicated delivery, with a low birth weight at 5lb 4oz.

At three months of age she was referred to the children's hospital following a one-month history of intermittent fever with irritability, a high-pitched cry, questionable seizure activity, and increasing dystonic posturing with CSF leukocytosis and negative TORCH titers. She presented with a tentative diagnosis of aseptic or viral meningitis and markedly abnormal CT and MRI indicating intracranial calcifications and severe white matter disease. EEG showed asymmetries, discontinuous background activity and multifocal sharp wave activity. The infant was also diagnosed with severe cortical visual impairment and hypothyroidism. CSF was found to have high levels of neopterin.

Based on clinical, neuroimaging, and CSF findings, the diagnosis of Aicardi-Goutieres syndrome was made.

Discussion

There has been great progress in recent years in the elucidation of the pathophysiological mechanisms likely to cause AGS, spurred by the identification by Crow et al in 2006 of four distinct genes involved. Mutations were identified in the three prime exonuclease 1 (TREX1) gene, and in the genes encoding the three subunits of the hetero-trimeric ribonuclease H2 complex (RNASEH2A, RNASEH2B, and RNASEH2C)[5]. It is hypothesized that nuclease dysfunction leads to an accumulation of endogenous nucleic acids, triggering an inappropriate IFN-α mediated innate immune response. The cascade of inflammatory mediators produced by immune cells is then thought to mediate the tissue damage, calcification, and microangiopathy seen in AGS[1]. This hypothesis accounts for the phenotypic similarities between AGS and congenital TORCH infections, where an innate immune response is triggered by the presence of viral nucleic acids. More recently, a fifth mutation has been identified in the SAMHD1 gene in AGS patients. The function of SAMHD1 is not yet clear, but involvement in the innate immune response has been implicated[1]. While the genes involved indicate the important role of the immune system in AGS

pathogenesis, it is not clear why the response seems to cease after a few months.

It is not clear if findings documented in a limited number of cases are part of the AGS phenotype or unrelated processes. AGS has been previously reported with cortical visual impairment and hypothyroidism (which were identified in our patient), as well as scoliosis, IDDM, hemolytic anemia, polygammaglobulinemia, neonatal cardiomyopathy, demyelinating peripheral neuropathy, and congenital glaucoma[2]. Neuroimaging findings that have been documented in a few cases include callosal dysgenesis, and brain stem and cerebellar atrophy[3].

Differential diagnosis of AGS can be challenging. AGS is relatively rare and patients present with a somewhat variable phenotype that has not yet been clearly defined. Many patients may remain unidentified after their condition is misdiagnosed as the sequelae of congenital infection. Although few treatment options for AGS have been proposed, appropriate diagnosis is important due to the high risk of recurrence. Patients diagnosed with AGS may also benefit from

initiation of respiratory and swallowing therapy, as pneumonia represents a significant source of morbidity and mortality in these patients. It has also been suggested that parents who are carriers of the TREX1 mutation may be at slightly increased risk for the development of systemic lupus erythematosus or retinal vasculopathy with cerebral leukodystophy, though these associations are not yet well-studied.[6] Awareness of the typical neuroimaging findings in AGS is the key to appropriate diagnosis and counseling.

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Aplasia of the parotid glands with accessory parotid tissue

Abstract

Congenital absence of the parotid gland is a rare entity. Absence is most commonly unilateral, and is not associated with accessory glandular tissue. In the majority of reported cases, parotid gland aplasia is seen with craniofacial abnormalities or hypoplasia of other ectodermal structures, particularly the lacrimal glands. We present a 14-year-old male with bilateral parotid gland aplasia detected incidentally on MRI of the brain and then confirmed on neck CT. The studies also revealed accessory parotid tissue superficial to the left masseter muscle. There were no associated craniofacial abnormalities. The lacrimal glands and submandibular glands were normal.

Introduction

The parotid gland is the largest salivary gland and is anatomically divided into superficial and deep lobes by the facial nerve and its divisions. The superficial lobe composes the majority of the gland and lies superficial to the masseter muscle and the ascending ramus of the mandible. The deep lobe of the gland extends through the stylomandibular tunnel and protrudes into the prestyloid parapharyngeal space. Approximately 20% of normal individuals also have acces- sory parotid tissue, which lies superficial to the masseter muscle and several millimeters anterior to the main parotid gland [1]. There are only three previously reported cases of accessory parotid tissue associated with aplasia of the main parotid gland [2–4]. Functionally, the parotid glands serve as a major source for saliva in the oral cavity. Absence or dysfunction of the parotid glands leads to variable degrees of xerostomia and its associated complications. Chronic xerostomia commonly causes symptoms of dysphagia, hoarseness, oral candidiasis, dental caries, halitosis and periodontal disease.

Absence of the parotid gland is rarely reported. Unilateral or bilateral aplasia of the parotid gland has been reported by several authors,

sometimes occurring as a familial trait [5]. The vast majority of reported cases are unilateral and associated with other congenital anomalies. We present a case of isolated bilateral parotid gland aplasia with associated accessory tissue identified by CT and MRI in a 14-year-old male with a history of xerostomia and dysphagia.

Case report

A 14-year-old boy presented to our hospital with persistent daily emesis for over a year. The patient's medical history included chronic xerostomia and dysphagia. A brain MRI without contrast was ordered to examine the brain for central pathology that could cause vomiting. A contrast- enhanced MRI incidentally revealed bilateral aplasia of the parotid glands with associated accessory parotid tissue present on the left and a normal brain (Fig. 1). Contrast- enhanced CT of the neck confirmed the presence of the submandibular glands and bilateral absence of the parotid glands with unilateral left accessory parotid tissue (Fig. 1). A segment of the left Stensen's duct is appreciable on CT, while the right duct is absent (Fig. 2).

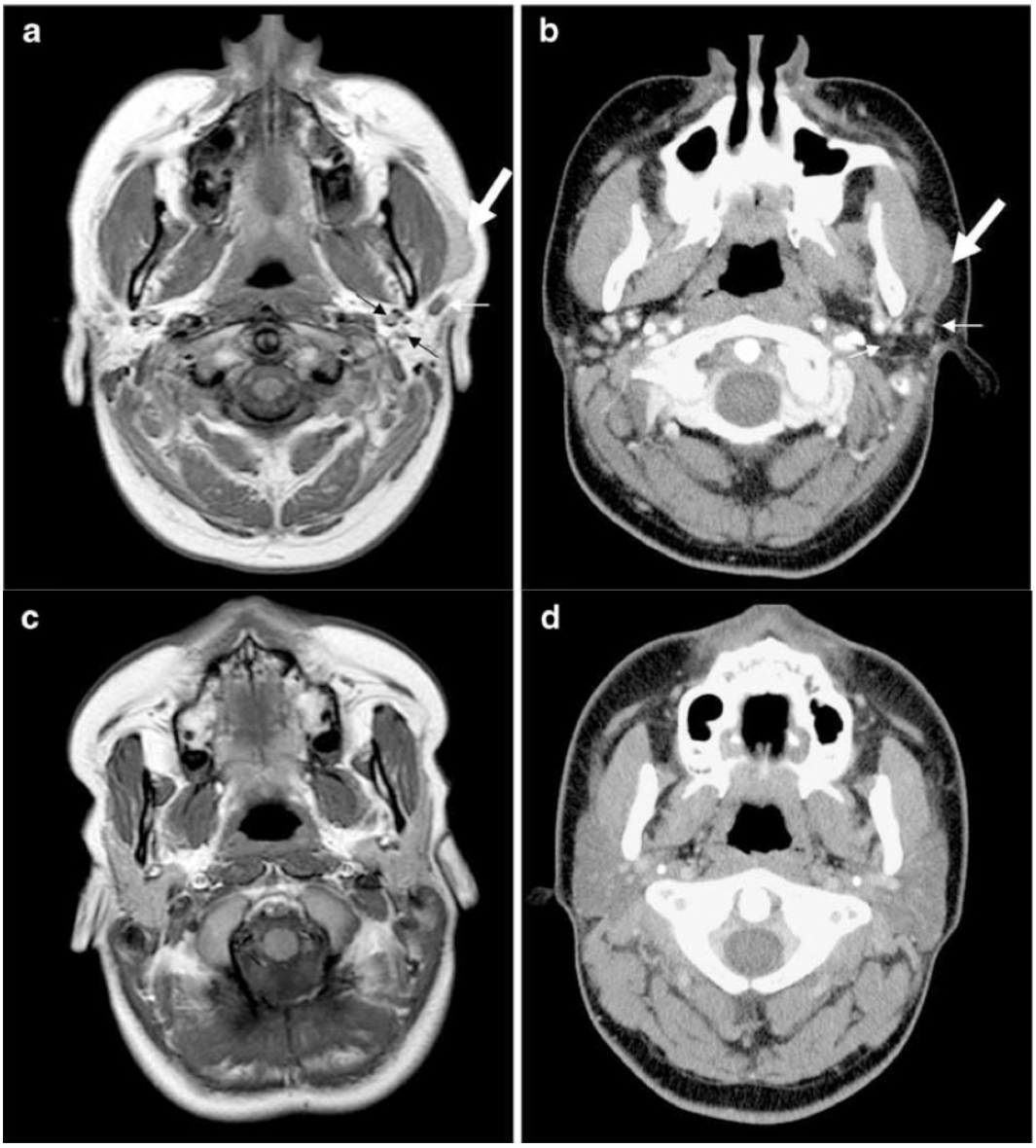

Fig. 1 Axial MRI (a) and CT (b) images at the level of the angle of the mandible show bilateral absence of parotid glands with accessory parotid tissue on the left (large arrow). Within the parotid space, there is adipose tissue in addition to normal lymph nodes (small arrows) and vascular structures. Axial CT and MRI of a normal patient are shown for comparison (c, d)

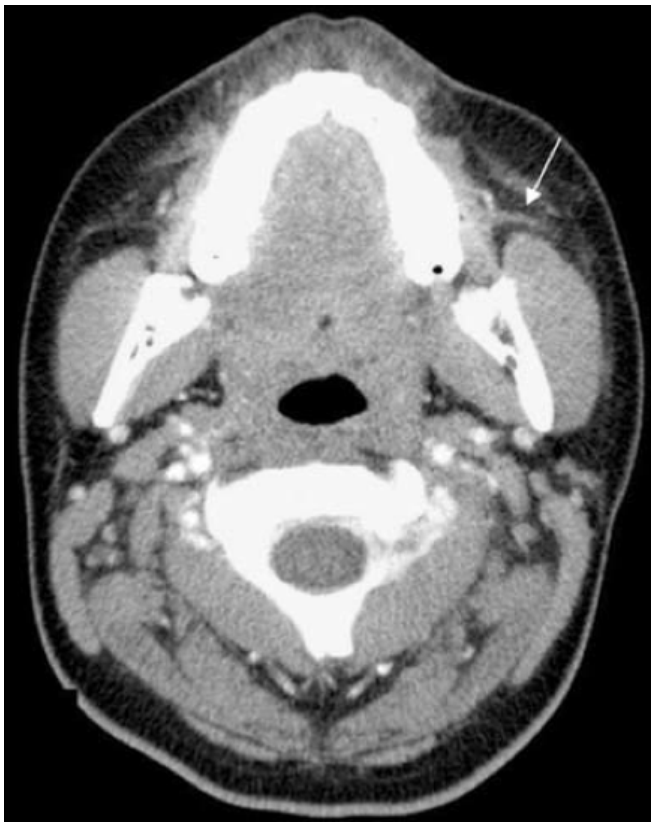

Fig. 2 There is a normal-appearing left Stenson's duct (arrow). The right Stenson's duct is not visualized.

Discussion

The primordial parotid glands are the first salivary glands to appear in embryonic development, at 4–6 weeks of gestation. They arise from a proliferation of the oral epithelium, which is of ectodermal origin. Disruptions in embryonic development of the parotid glands most commonly appear to be unilateral and affect multiple ectoderm-derived structures in the region. Parotid gland aplasia, when present, is rarely bilateral and usually coexists with hypoplasia of other salivary glands or the lacrimal glands, or with various cranio-oral malformations. The majority of cases of parotid aplasia have been reported with associated cleft lip/palate, lacrimoauriculodentodigital (LADD) syndrome, hemifacial microsomia, mandibulofacial dysostosis, or other congenital anomalies of the first and second branchial arches [2, 6, 7].

During normal embryonic development, the parotid gland is the last salivary gland to become encapsulated. Consequently, several structures become embedded within
the substance of the gland. Despite the close approximation of these tissues during embryonic development, the normally embedded structures appear to be unaffected by aplasia of the parotid gland. In our case, there is no apparent change in the structure or function of

the facial nerve or its branches. The retromandibular vein, external carotid artery, and associated vascular branches also appear normal. Parotid and periparotid lymph nodes are present (Fig. 1).

Accessory parotid tissue is found, usually unilaterally, in approximately 20% of the normal population [1]. Its anatomy is described in detail by Currarino and Votteler [8]. Accessory tissue is histologically and radiologically similar to normal parotid tissue, and is susceptible to similar pathology (1–7% of parotid neoplasms originate in acces- sory parotid tissue) [8]. Radiologic assessment of accessory parotid tissue can have important clinical and surgical implications in patients with associated pathology. In the current case, the accessory parotid tissue communicates with an intact segment of Stensen's duct. This is the fourth reported case of accessory parotid tissue associated with aplasia of the ipsilateral main parotid gland [2–4].

Clinically, absence or dysfunction of the parotid glands leads to varying degrees of xerostomia and, when chronic, can be associated with dysphagia, hoarseness, oral candidiasis, dental caries, halitosis and periodontal disease. The goal of treatment is to prevent these sequelae by maintaining the moisture of the oral mucosa, improving dental hygiene, and maintaining normal oral bacterial flora. A number

of saliva substitutes are currently available for treatment of xerostomia. Many commonly used drugs can exacerbate xerostomia and should be avoided when possible. These include various antihistamines, decongestants, analgesics, antidepressants, and bronchodilators, to name a few. Risk of caries may be further minimized by rigorous attention to oral hygiene and placement of dental sealants.

Imaging is imperative for diagnosis of salivary gland aplasia. CT and MRI allow for noninvasive assessment of abnormalities of the major salivary glands.

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