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Oro-Facial-Digital Syndrome IX With Severe Microcephaly: A New Variant in a Genetically Isolated Population

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We describe four patients, two pairs of siblings, with a somewhat unique oro-facial-digital syndrome. The siblings come from the Navajo population which has undergone several genetic "bottlenecks." Thus, as would be anticipated, this syndrome seems to show autosomal recessive inheritance. The combination of the presence of retinal colobomata and the paucity of digital findings in these patients leads us to believe that their condition is best described as a variant of oro-facial-digital syndrome IX. In addition to retinal colobomata, these patients also show severe microcephaly, mental retardation and short stature. © 2007 Wiley-Liss, Inc.

Key words: genetic isolates; Navajo; oro-facial-digital syndrome; retinal colobomata; microcephaly

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INTRODUCTION

The Navajo American Indians went through a number of population "bottlenecks" (periods of reduced population such that future generations are descended from a limited number of people) during their migrations and encounters with European peoples. Although they have strong taboos against consanguinity (clan exogamy is strictly observed), the tribal members share many rare recessive alleles, likely as a consequence of population explosions after these bottlenecks. During the last several decades, four Navajo-limited or Southwestern Athabaskan-limited diseases have been described, including forms of severe combined immunodeficiency (SCID), an unusual neuropathy with liver disease, a poikiloderma resembling Rothmund–Thompson syndrome, and a type of brainstem dysgenesis [Erickson, 1999]. We now provide a description of an apparently unique form of oro-facial-digital syndrome among the Navajo.

There are multiple forms of Oro-facial-digital syndrome (OFD). Although considerable heterogeneity exists [Toriello, 1988], most are autosomal recessive. However, we believe that the form of OFD with severe microcephaly found among the Navajo is unique. Because of the low frequency of "digital" anomalies and the presence of retinal colobomas, we believe that this variation of the syndrome should be included with those of OFD IX.

CASE REPORTS

Patient 1 was a 3.352 kg product of an uncomplicated pregnancy to a gravida 3, para 2, Navajo woman. Of note, is that an older sister to this patient had died at 6 months of age of the "same condition." At birth, the patient showed a bifid tongue, high palate with submucous cleft, clinodactyly, hexadactyly and meso-brachyphalangia of both hands, absent clitoris, anomalous vaginal mucosa, severe microcephaly, oral labial hematoma, and hypertonia. A karyotype was performed and was 46, XX. Her neonatal history was complicated by multiple episodes of respiratory distress and it was noted that it was difficult to place a nasotracheal tube because of "unusual pharyngeal anatomy." There were seven hospitalizations for respiratory distress by 6½ months of age. A pediatric

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geneticist thought she met the criteria for Smith-Lemli-Opitz syndrome Type 2, and this was the diagnosis that she carried for some years. A cardiac evaluation and a renal ultrasound provided normal results. The accessory post-axial digits were removed shortly after birth. Other workup included an MRI showing diffuse ventricular dilation, non-specific bilateral hippocampal atrophy and a "definite small focal area of grey matter heterotopia in the subependymal region of the right occipital horn of the lateral ventricle". At age 4, Duane Syndrome Type 1 was diagnosed because of eye movement problems, especially with lateral gaze. At the time of this diagnosis, she remained severely mentally retarded, with severe microcephaly. A cleft of the lower alveolar ridge at the canine tooth level was also observed. Small colobomas of the retina were noted but vision was thought to be normal. An exam at 15 years of age showed marked short stature (height age of 10 years). Ophthalmological exam questioned whether there was some optic atrophy and noted the small retinal colobomas located inferior to each optic nerve head. Also at 15 years of age, it was noted that the fourth and fifth metatarsals were shortened. Hamartomas of the tongue and bifid tongue persisted (Fig. 1). Her MRI findings were characterized by decreased cerebral white matter, particularly prominent in the region of the trigone of the lateral ventricles. There was diffuse cerebellar hypoplasia/atrophy. The chief finding was the presence of bilateral, more or less symmetrical, gray matter heterotopias in a subcortical band-like distribution in the anterior 2/3 of the lateral ventricles and a nodule of heterotopic gray matter in the trigone of the lateral ventricle on the right.

Patient 2, the younger sister of Patient 1, was the 3.579 product of an uncomplicated pregnancy to a now gravida 4, para 3, living children 2, Navajo woman. At birth, microcephaly, notched alveolar dental ridge and a high arched palate were noted. A submucous cleft of the hard palate, a tight frenulum with bifid anterior tongue, and clinodactyly were also seen. Because of similarities to her sister, she also carried the diagnosis of Smith-Lemli-Opitz syndrome Type 2 for some time. She did not have the visual problems or colobomata that were noted in her sister. She had hamartomas of the edge and lower surface of her tongue and shortened third, fourth and fifth metatarsals and shared severe microcephaly and mental retardation with her sister. She was also far less than 2nd centile for height. Her MRI showed less severe migrational abnormalities than those of her sister.

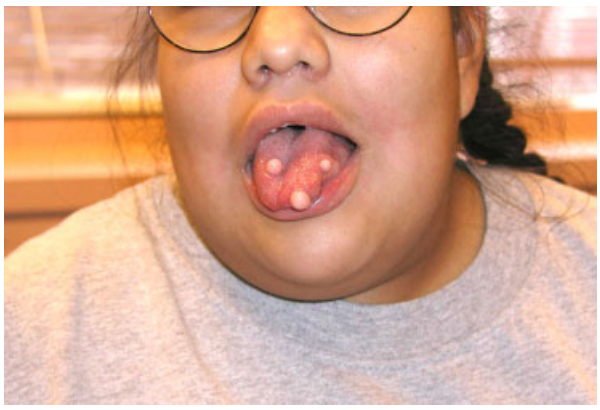

FIG. 1. Oral lesions in Patient 1 at 15 years of age. [Color figure can be viewed in the online issue, which is available at www.interscience.wiley.com.]

Patient 3 was the 2.430 kg product of an uncomplicated pregnancy to a gravida 1, para 1, Navajo woman. She had a number of birth defects that led to the diagnosis of CHARGE syndrome, including hydrometrocolpos with vaginal agenesis, microcephaly, ventricular dilation, hypoplastic cerebellum, bilateral colobomas of the choroid, bilateral mild hearing loss and abnormal ears. The CHARGE syndrome was then considered a familial disorder when her brother (Patient 4) was born with similar features. She did not have recorded oral hamartomas but had severe microcephaly and mental retardation as did her brother. Her eye problems were choroidal colobomas associated with alternating exotropia and nystagmus. Karyotype, many routine laboratory tests, and transferrin isoelectric focusing were normal. At 18 years of age, she had a height of 142 cm (less than 5th centile), she was 50th centile for weight and her head circumference measured 49.8 cm (50th centile for 27 months of age). Her tongue was bifid with a fairly deep groove down the middle. Her teeth were crowded and irregular. There was suggestive brachyphalangia (Fig. 2A). Her MRI showed changes consistent with migrational abnormalities.

Patient 4 was the product of a second pregnancy to Patient 3's mother. The pregnancy was complicated by herpes, which led to a Cesarean section. Birthweight was 3.006 kg with a length of 51 cm and a head circumference measuring 32 cm. He was noted to have abnormal ears, redundant growth on the left side of the tongue, a cleft of the alveolus and maxillary gingival ridge, a broad nasal bridge and small penis. Retinal colobomas were noted early in life. He was considered to have familial CHARGE syndrome because of overall similarity to his sister. He had a Nissen fundoplication with a G-tube placed and was hospitalized twice in the first year of life for pneumonia and bronchiolitis. An early MRI disclosed diffuse cerebral dysplasia with an unidentified corpus callosum. A lingual frenulum and a hemartoma measuring 4 mm in diameter on the left side of the tongue were excised at 1 year of age. Cardiologic and audiologic evaluations were normal. A coloboma of the retina, approximately one quarter of the diameter of the optic disk, was found in the right eye while two pinhead-sized similar lesions of the retina were found in the left eye. His karyotype

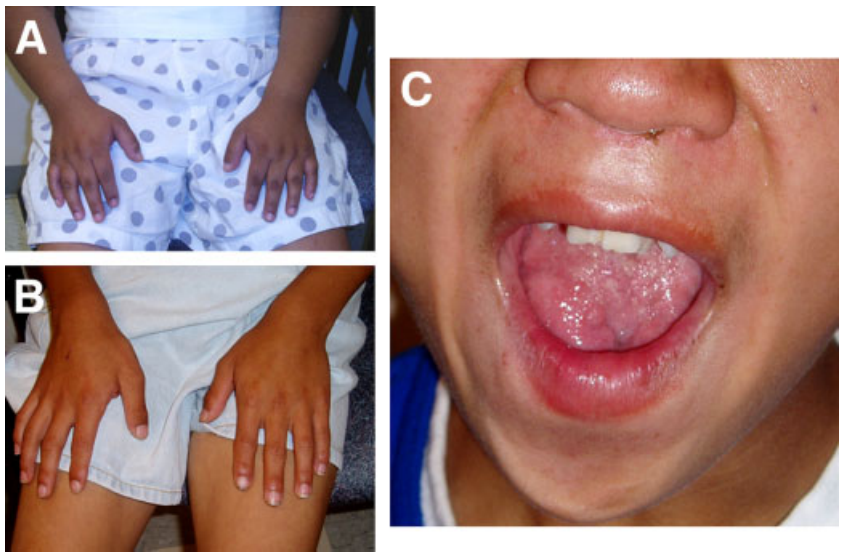

FIG. 2. Hands of Patient 3 (**A**) and Patient 4 (**B**) and mouth of Patient 4 (**C**). [Color figure can be viewed in the online issue, which is available at www.interscience.wiley.com.]

was also normal. At age 15 years, he had developed further than his sister and was speaking in three to four word sentences. He had a height of 155 cm (less than 5th centile and 15th centile for 11½ years of age) and his head circumference measured 48.5 cm (less than 5th centile and 50th centile for 15 months of age). His tongue had a very deep groove with a bifid tip (Fig. 2C), the palate was unusual with tenting and ridging and the upper alveolar ridge showed very irregularly crowded teeth. At that time, his penis was not markedly decreased in size. Digital or tarsal abnormalities were not noted (Fig. 2B). His MRI showed changes compatible with migrational abnormalities.

DISCUSSION

As summarized in Table I, constant features in these patients are bifid tongue, microcephaly, and short stature. Digital features are less common. Three of the four patients have retinal colobomata. Other oral anomalies have included hamartomas (3/4), cleft alveolar ridge (3/4) and abnormal frenula (2/4). The digital abnormalities have been less complete or less noted: polydactyly in one case and tarsal/carpal shortening in two cases. The microcephaly has been accompanied by brain atrophy and migrational abnormalities.

This constellation of signs shows marked overlap with Oro-facial-digital Syndrome IX (OFD IX). This was originally described in two boys, one with lobulated tongue [Gurrieri et al., 1992]. The boys were mildly mentally retarded and showed slightly notched upper lips. They also showed retinochoroidal colobomas. Nevin et al. [1994] and Sigaudy et al. [1996] reported female cases suggesting autosomal recessive inheritance. Slight clefts or notching of the upper lip suggested a similarity to oral-facial-digital syndrome II [Reardon et al., 1989]. Sigaudy et al.'s [1996] case had brain atrophy while a case reported by Nagai et al. [1998] had Dandy-Walker malformation and retrobulbar cysts. Other cases reported by Jamieson [1993] and Stevens and Marsh [1994] are also tabulated for comparison to our cases. Our patients do not share the notching of the upper lip seen frequently in OFD IX but do share the retinal colobomas and paucity of digital findings. Their microcephaly and mental retardation is more severe than is seen in OFD IX. Of the other oral-facial-digital syndromes, type IV usually has cerebral anomalies [Digilio et al., 1995; Toriello et al., 1997] but also has tibial shortening, which our patients lack, and does not have retinal colobomata. Type VI usually has mental retardation but cerebellar anomalies and "central polydactyly" make it quite different that what is seen in our patients [Toriello, 1993].

A major event in the history of the Navajos was their forced relocation, the "Long Walk" to Fort Sumner, New Mexico (located at Bosque Redondo, where a memorial has recently been built), which resulted in many Navajo deaths [Williams, 1992]. The famous hunter/trapper Kit Carson aided the U.S. Army in 1863–1864 in rounding up the Navajos in an attempt to pacify them. The years at Fort Sumner were tragic, with draught and infestations causing famine and an epidemic of small pox resulting in the death of at least 2,000 individuals. After a period of 4 years, the Navajos were allowed to return to their traditional lands, but only approximately 8,000 Navajos returned from this devastation (and the tribe had a low point of 5,000 in the "camp" [Williams, 1992]).

TABLE I. Features of Patients and Literature Review

	Oro-facial					Digital				CNS				Other	
Patient	Oral hamartomas	Bifid tongue	Cleft palate (including submucous)	Cleft alveolar ridge	Excess or short frenula	Polydactyly	Brachyphalangia	Tarsal/carpal shortening	Camptodactyly	Microcephaly	Brain atrophy	Duane syndrome	Retinal colobomata	Migrational abnormalities	Absent clitoris	Short stature
1 ♀	+	+	+	+	?	+	+	+	+	+	+	+	+	+	+	+
2 ♀	+	+	+	+	+	−	?	+	−	+	?	−	−	+	−	+
3 ♀	−	+	−	−	−	−	−	?	−	+	+	−	+	+	−	+
4 ♂	+	+	−	+	+	−	−	?	−	+	+	−	+	+	N/A	+
Literature[a]	7/7	3/7	1/7	?	6/7	1/7	2/7	?	1/7	4/6	3/4	?	7/7	4/6	0/2	4/6

[a]Gurrieri et al. [1992], Jamieson [1993], Nagai et al. [1998], Nevin et al. [1994], Stevens and Marsh [1994].

The actual breeding population among those 8,000 returning to the tribal lands would, of course, be much smaller, because as much as one-fourth of the population might have been past breeding age and as much as one-half of this population might have been children. The nearly quarter of a million Navajos now registered with the tribe are descended from that portion of the population and from the small number of Navajos who successfully hid from the U.S. Army in lands that are now on the Western Reservation.

These events have led the Navajo to carry unique alleles of several recessive diseases: metachromatic leukodystrophy [Pastor-Soler et al., 1994] and Navajo Neurohepatopathy [Karadimas et al., 2006]. Other autosomal recessive diseases first described or of increased frequency among the Navajo have not yet been cloned: Microvillus Inclusion Disease [Pohl et al., 1999] and Poikiloderma with neutropenia [Wang et al., 2003]. Still other rare recessive diseases share unique alleles with the Apaches who shared an earlier "bottleneck" with the Navajo [Erickson, 1999]: severe combined immunodeficiency [Li et al., 2002] and HOXA1 deficiency (formerly known as Athabaskan Brainstem Dysgenesis [Tischfield et al., 2005]). We believe this variant of OFD IX is a further example of a rare autosomal recessive disease with a unique allele of increased frequency in the Navajo.

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