Acrocallosal Syndrome: A Case Report and Literature Survey

Brian D. Hodgson, DDS
Lindsey Davies, DDS
Cesar D. Gonzalez, DDS, MS

ABSTRACT

Acrocallosal syndrome (ACS) is a rare, genetically transmitted disorder characterized by facial deformities. These include a large forehead, large anterior fontanelle, broad nasal bridge with increased intercanthal distance, partial or complete agenesis of the corpus callosum, polysyndactyly, polydactyly, and mental retardation. Limited information concerning the dental development and treatment has been published. In addition to the classic facial deformities aforementioned, the other most commonly reported oral findings are: short philtrum/upper lip (30%); high-arched palate (30%); cleft lip/palate (20%); micro/retrognathia (13%); open mouth (15%); thin lips (11%); and 1 report of over-retained primary teeth. Seizure disorders are also a common finding due to the neuroanatomical deformities associated with this disorder. The purpose of this report was to describe the case of a 7-year-old male child with acrocallosal syndrome who presented with a cleft lip and palate, hydrocephalus, a seizure disorder, and delayed exfoliation of his primary dentition and was observed for 4 years. A review is conducted to present the pertinent medical literature concerning the oral findings associated with ACS. Dental management of this case and possible contributing factors of delayed exfoliation/permanent tooth eruption are also discussed.
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KEYWORDS: ACROCALLOSAL SYNDROME, CHROMOSOME 12, POLYDACTYLY, CORPUS CALLOSUM ABNORMALITIES, MENTAL RETARDATION, CRANIOFACIAL ABNORMALITIES

Acrocallosal syndrome (**ACS**) was first reported by Schinzel in 1979.[1] Since then, there have been over 60 cases reported in the medical literature. Courtens et al[2] proposed that at least 3 of 4 diagnostic criteria be met for ACS diagnosis, including:

1. total or partial absence of the corpus callosum;
2. minor craniofacial anomalies (prominent forehead, hypertelorism, short nose with anteverted nostrils, and large anterior fontanelle);
3. moderate to severe psychomotor retardation (with hypotonia); and
4. polydactyly.

Synonymous terms for ACS include: ACS-Schinzel type; Schinzel syndrome I; ACLS; and absence of the corpus callosum with unusual facial appearance, mental deficiency, duplication of the halluces, and polydactyly. Originally, this syndrome was suggested to be caused by a dominant mutation,[3] but subsequent case reports demonstrated an autosomal recessive inheritance pattern due to the recurrences in families and parental consanguinuity.[4,5,49]

Dr. Hodgson is assistant professor, Program in Pediatric Dentistry, Department of Developmental Sciences, School of Dentistry, Marquette University, Milwaukee, Wis, and is attending dentist, Pediatric Dentistry Residency Program, Children's Hospital of Wisconsin, Milwaukee; Lindsey Davies was dental student, and Dr. Gonzalez is associate professor, Program in Pediatric Dentistry, Department of Developmental Sciences, both in the School of Dentistry, Marquette University.

Correspond with Dr. Hodgson at brian.hodgson@marquette.edu

When faced with treating ACS patients, dental practitioners have little published information to draw upon. Only 1 dental case report concerning ACS has been published in the scientific literature.[6] In addition to the aforementioned pathognomonic findings, Shilpa et al. described an 8 year-old male with a chief complaint of over-retained primary teeth and severe crowding of the maxillary and mandibular anterior permanent teeth. All 4 permanent first molars were erupted, but there were over-retained primary incisors with the eruption of the permanent incisors. Also noted were a high-arched palate and an Angle's Class I molar relationship.

The purpose of this paper was to provide a dental case report of acrocallosal syndrome and to review relevant published medical literature for other commonly reported oral findings.

CASE DESCRIPTION

A 7-year, 6-month-old male patient reported to the pediatric dentistry clinic of the School of Dentistry, Marquette University, Milwaukee, Wis, for an initial exam. He was born at full-term without complications, and there has been no known consanguinity established between the mother and father. The medical history revealed multiple previous surgeries completed at Children's Hospital Boston, Boston, Mass, where the diagnosis was originally established. These surgeries included procedures to correct hand and feet polysyndactyly and polydactyly and closure of the left lip and palatal clefts. Hydrocephalus was corrected with a ventral-peritoneal shunt but was later revised to a ventral-atrial shunt. The patient was diagnosed with a seizure disorder and thyroid hypoactivity for which depakote (valproic acid) and levothyroxine sodium have been taken daily. The patient displayed significant cognitive developmental delays, was nonverbal, and required a walker to ambulate. The parents' chief complaint was unexfoliated primary teeth. Pain was not reported, and the patient had little difficulty eating a modified diet (thickened liquids and food cut into small pieces) due to delayed oromotor response.

The extraoral clinical exam revealed a dysmorphic head with macrocephaly and a large forehead, wide intercanthal distance, a broad, flat nose, low set ears, a surgically repaired cleft lip, and a long philtrum. Figure 1 shows a 3D CT scan of the facial skeletal structures. Evident in this picture are the wide intercanthal distance, large forehead, broad nasal bridge, and alveolar cleft. The intraoral exam revealed a complete primary dentition, slightly delayed for age, with the exception of a missing maxillary left primary lateral incisor due to the alveolar cleft. There were no visible cavities and the parents were providing excellent oral hygiene with minimal gingivitis noted. The soft tissue exam revealed a left alveolar/gingival cleft, high-arched palate, open

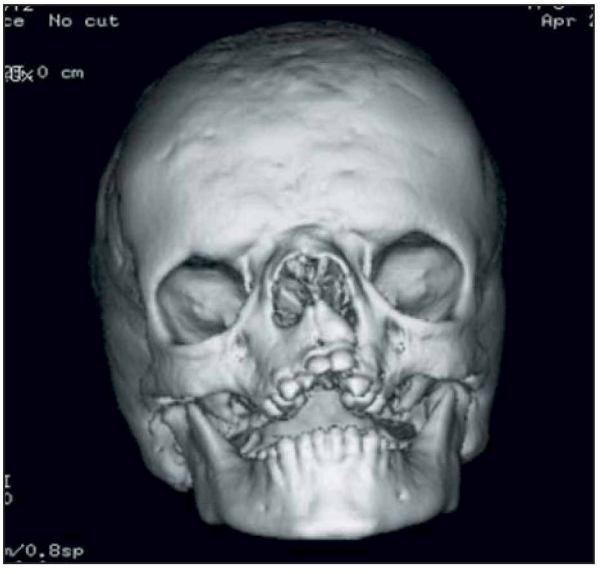

Figure 1. 3D CT image of facial skeletal structure of the Acrocallosal syndrome. Note the enlarged forehead, broad nasal bridge, increased intercanthal distance, and left alveolar cleft.

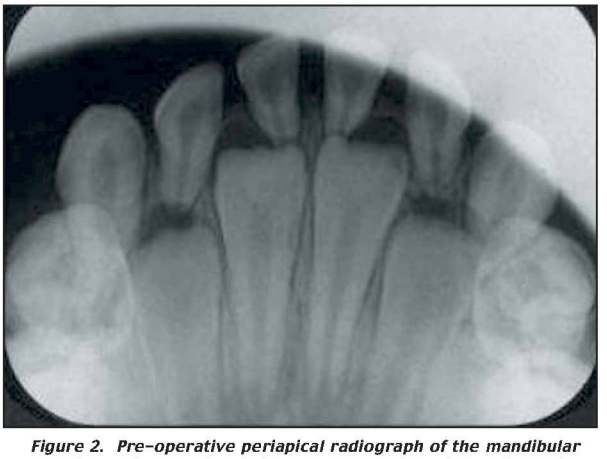

Figure 2. Pre-operative periapical radiograph of the mandibular anterior region showing limited root resorption of the primary incisors and progressing root formation of the permanent incisors.

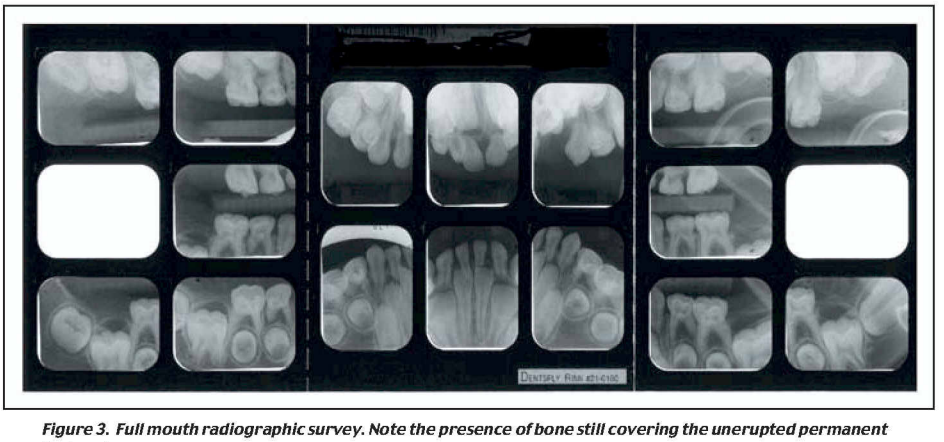

Figure 3. Full mouth radiographic survey. Note the presence of bone still covering the unerupted permanent first molars.

mouth at rest, and drug-induced gingival enlargement. There was no mobility noted with any of the teeth. The patient demonstrated a mild drooling habit, with the salivary flow and consistency within normal limits.

The parents reported that the patient's primary dentition did not begin to erupt until he was approximately 18 months of age, and the eruption pattern had been severely delayed for the remaining teeth. Since the patient was still within the normal age range for initiation of the first transition, a recommendation was made to observe the natural exfoliation process to start. The gingival enlargement was discussed as a possible contributing factor to the delayed eruption. The topic of surgical correction of the gingival overgrowth was broached, but the parents declined this option due to the probable re-currence of the overgrowth and their perception of a poor risk/benefit ratio.

The patient returned for recall examinations twice per year as recommended. After 3 years of observation, the primary teeth had not exfoliated and were not significantly mobile on clinical exam. A mandibular anterior periapical radiograph was obtained that demonstrated advancing root formation of the permanent incisors with mild resorption of the roots of the primary incisors (Figure 2). After a discussion of the risks and benefits, a decision was made to extract the mandibular anterior primary incisors to allow the permanent mandibular incisors to erupt. Due to uncooperative patient behavior secondary to mental retardation, general anesthesia was recommended to complete care.

The patient was admitted to Children's Hospital of Wisconsin, Milwaukee, Wis, for ambulatory surgery. With the patient at an adequate plane of general anesthesia via the orotracheal route (nasal deformities ruled out nasal intubation), a full-mouth radiographic survey consisting of 16 films was obtained (Figure 3). This survey reveals the presence of all permanent teeth, except for the maxillary left primary and permanent lateral incisors, the maxillary right permanent canine and lateral incisor, and the maxillary left permanent second bicuspid. Unfortunately, the patient's high-arched palate and constricted maxilla prevented ideal placement of the radiographic films, so the information available from these films does not allow comment on the presence of the maxillary third molars, or the root development of any of the maxillary dentition.

The location of the orally placed endotracheal tube did not permit the capture of the permanent mandibular left third molar area, but there is no evidence of a crypt or calcification of the permanent mandibular right third molar. The positions of the permanent maxillary left and mandibular right and left second molars may have inhibited the eruption of the adjacent permanent first molars.

Absence of root formation of the permanent mandibular bicuspids is evident, and the mandibular second bicuspids appear to be angulated in either a buccal or lingual direction. All 4 permanent first molars were unerupted and covered by bone with follicular spaces that appear enlarged but were not suspected of undergoing cystic transformation. Advanced root development of the permanent mandibular incisors is present. The primary maxillary central incisors appeared to have root resorption progressing, and these teeth were slightly mobile. The interproximal cortical bone appears appropriate, and the remaining bone density, furcational bone, and trabeculation pattern appear unremarkable. The root morphology of the primary dentition appears normal. The root formation of the mandibular first molars is delayed but progressing.

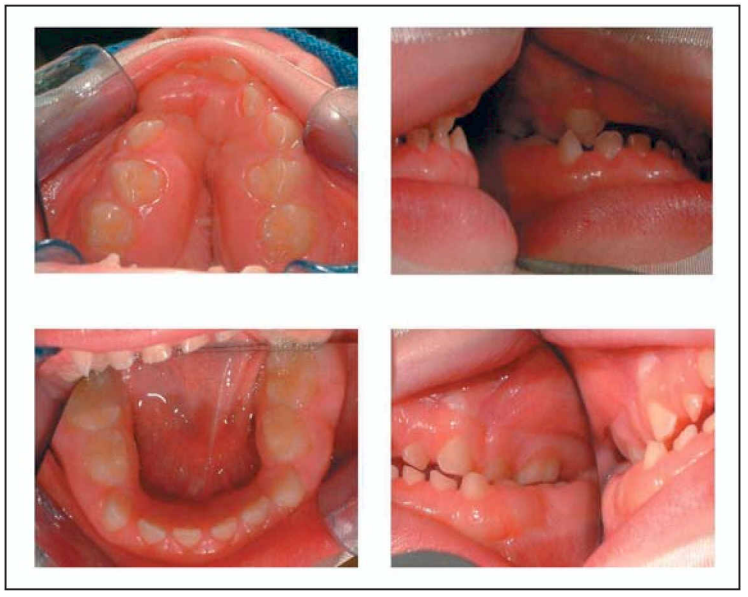

Figure 4. Clinical photographs of the arches and posterior occlusion. Note the high arched palate, asymetric mandibular arch, over-retained primary incisors, posterior cross bites, and unerupted permanent first molars.

Clinical photographs of the patient's dental arches and occlusion were taken (Figure 4). The photos demonstrated a high-arched, narrow palate with left clefting, a bilateral posterior crossbite, and generalized bulbous gingival over-growth that does not affect function or esthetics. No cavities were noted clinically or radiographically. After consulting with the parents, the decision was made to continue with the initial treatment plan of extracting the mandibular incisors only and allowing the maxillary incisors to exfoliate naturally. All four primary mandibular incisors were then extracted without complication, adequate hemostasis was obtained, and the patient recovered from the general anesthetic. Postoperative healing of the extraction sites occurred without complication.

A 1-month follow-up appointment revealed that the permanent mandibular incisors had still not erupted (Figure 5). The agreed-upon treatment plan was to continue to observe for

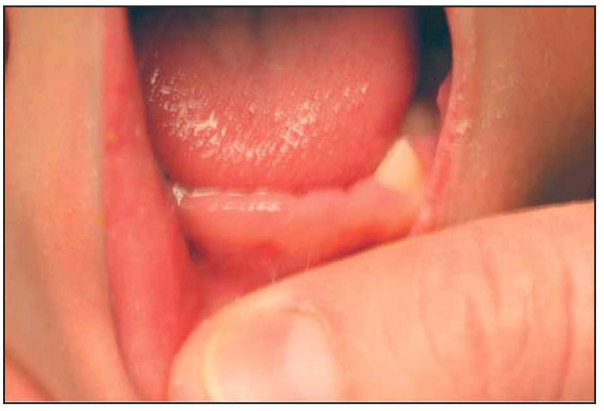

Figure 5. One month post extraction photograph showing lack of eruption of the permanent incisors.

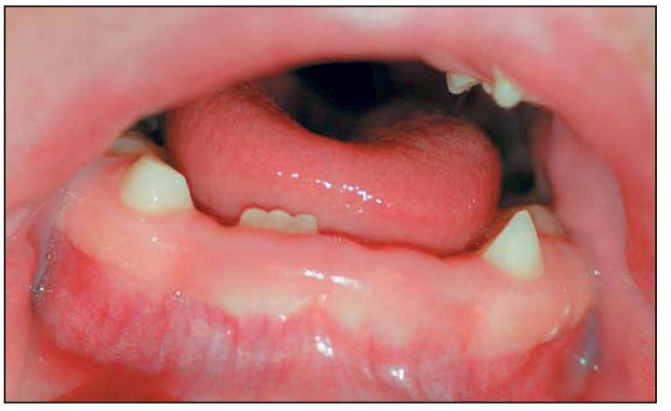

Figure 6. Nine month follow-up photograph demonstrating the eruption of the mandibular right permanent central incisor.

exfoliation of the maxillary teeth and eruption of the mandibular incisors. The parents declined to consider further extractions due to the possibility that other permanent teeth may not erupt, leaving the child with compromised chewing ability. At the next recall appointment, approximately 9 months after the surgery, the permanent mandibular right central incisor had erupted (Figure 6). At 16 months, the permanent mandibular left central incisor had erupted.

LITERATURE REVIEW

A Medline/Ovid and PubMed search was conducted using the term "acrocallosal syndrome," with the aforementioned synonymous terms used as the keywords, and the results were reviewed for inclusion. Forty-one articles describing 61 ACS cases were identified and included in this review. The oral findings are summarized in Table 1, with the most common findings associated with the oral cavity being a short philtrum/upper lip (30%), followed by a high-arched palate (30%), cleft lip/palate (20%), micro/retrognathia (13%), open mouth (15%), and thin lips (11%). All other findings occurred in less than 10% of the case reports.

Difficulty in collating these results was encountered due to the many synonymous terms utilized to describe oral findings. Also, clinical findings not associated with the oral cavity were the focus of many of the case reports. Males were affected in 61% of these cases, with the diagnosis made on 48 living patients[1-3,5-36] and on 13 patients who were aborted, still born, or who died shortly after birth.[18,26,30,37-42]

Courtens[2] proposed minimum required diagnostic criteria to identify minor craniofacial anomalies that most commonly include: macrocephaly; broad forehead with large anterior fontanelle; widely spaced eyes (often down-slanting); small nose with a broad nasal bridge; low-set, malformed ears, often with preauricular tags and epicanthal folds; and a high-arched or cleft palate. The required neurological findings are the partial or complete absence of the corpus callosum and mental retardation, and the musculoskeletal findings are severe muscular hypotonia, postaxial polydactyly of the hands and/or feet, and syndactyly of the fingers and/or toes. Other ACS characteristics listed include inguinal and umbilical hernias, seizure disorders, hypogenitalism/hypospadius, tapered fingers, and congenital heart defects. Other case reports include mild conductive or bilateral sensorineural hearing loss, narrow external meati of the ears, simian creases, frequent respiratory infections, and failure to thrive. Cystic malformations of the brain were recommended to be added to the list of frequent findings by Thyen et al.[22] An expected life span for ACS patients has not been suggested. Advanced medical support may allow these patients to survive well into adulthood.

DISCUSSION

ACS is categorized as a multiple congenital anomaly/mental retardation syndrome (**MCA/MR**).[5] Its name is derived from the terms acra (fingers and toes) and the corpus callosum[28] and involves deficits of both of these structures. There are no published incidence figures available, but ACS is classified as a rare disease by the National Organization of Rare Diseases as occurring with a frequency of less than 1 in 2,000 births.[43] The gene responsible for ACS is considered to be located on chromosome 12,[19] although some have suggested that it is a severe allelic form of Grieg cephalopolysyndactyly syndrome, the gene of which is on chromosome 13.[31]

Authors have identified ACS as having characteristics similar to a number of other syndromes, and have included in their lists of differential diagnoses following disorders: Greig cephalopolysyndactyly syndrome[4,9,10,12-15,17,21,22,28,31,37,38,50,51]; orofacial-digital syndrome type I,[17,38] II,[33,38] and VI[34]; Meckel-Gruber syndrome[15,38]; Smith-Lemli-Opitz syndrome[15,33,37,38]; Rubinstein-Taybi syndrome[33,38]; pseudotrisomy-13 syndrome[34]; trisomy 12p syndrome[19,27]; oropalato-digital syndrome II[33];

Reported Oral Findings

Author (s)		Cleft lip/palate	Short philtrum/upper lip	Long philtrum/upper lip	Smooth philtrum	High, arched palate	Micro/retrognathia	Down-turned mouth corners	Wide/large mouth	Small mouth	Hypoplastic teeth	Thin lips	Midline notch, upper lip	Thick lips	Open mouth	Hypersalivation	Exaggerated bow of upper lip	Notched tooth/teeth	Prognathism	Protruding tongue	Hypertrophic gingiva*	Upturned upper lip	Prominent lower lip	Hyperplastic alveolar ridges	Accessory gingival frenum	Hypoplasia of left alveolar ridge	Bi fid uvula	Redundant soft tissues at base of tongue	Prominent lateral palatine ridges	Broad gums	"Sagging" chin	Malalignment of incisors	Impacted permanent teeth	Over-retained primary teeth
Schinzel A, 1979			X			X									X		X																
Schinzel & Schmid, 1980	Case 1		X			X																						X		X	X		
(Previously reported above)	Case 2																																
Nelson et al., 1982	Case 1		X			X																											
	Case 2	X	X			X																											
Sanchis et al., 1985				X				X	X			X																					
Legius et al., 1985																																	
Schinzel & Kaufmann, 1986	Case 1	X	X					X																									
	Case 2		X					X		X																		X					
Philip et al., 1988	Case 1				X																												
	Case 2					X				X																							
Schinzel, 1988	Case 1		X				X	X																									
	Case 2																																
Salgado et al., 1989			X			X								X	X														X				
Temtany & Meguid, 1989						X																											
Moeschler et al., 1989																											X	X	X				
Casamassimo et al., 1989						X																	X	X	X								
Yuksel et al., 1990			X												X					X													
Hendriks et al., 1990																																	
Turolla et al., 1990				X		X	X					X										X											
Fryns et al., 1991	Case 1																																
	Case 2																																
Lungarotti et al., 1991				X		X									X																		
Gelman-Kohan et al., 1991	Case 1																																
	Case 2		X			X									X						X												
	Case 3		X												X						X												
	Case 4																				X												
Pfeiffer et al., 1992		X		X																													
Cataltepe & Tuncbilek, 1992						X														X	X												
Guion-Almeida & Richieri-Costa, 1992		X					X																										
Thyen et al., 1992			X			X																											
Sueldo & Fernandes, 1993		X										X	X					X															
Lurie et al., 1994			X																														
Christianson et al., 1994	Case 1		X											X			X	X															
	Case 2																X																
Baumstark et al., 1996	Case 2					X																											
Courtens et al., 1997		X					X																										
Bonatz et al., 1997																																	
Christianson et al., 2000	Case 1	X																															
	Case 2	X																															
Verloes & Lesenfants, 2000			X																														
Koenig et al., 2002	Case 1					X								X	X	X																	
	Case 2					X	X							X	X																		
	Case 3																																
Elson et al., 2002		X																															
Bijarnia et al., 2003	Case 1																																
	Case 2																																
Gulati et al., 2003							X																										
Gupta et al., 2003		X	X			X																											
Ikbal et al., 2004			X										X																				
Gul et al., 2004	Case 1		X						X		X																						
	Case 2						X																										
	Case 3					X																											
	Case 4											X																						
	Case 5											X																						
Steiner et al., 2004							X	X																									
Tastekin et al., 2005		X																															
Shilpa et al., 2006			X																														X
Hodgson et al., 2009		X		X		X									X																	X	X
		12	18	5	1	18	8	5	2	2	1	5	2	4	9	1	3	1	1	2	1	3	1	1	1	1	2	1	3	1	1	1	1	2
		21%	31%	9%	2%	31%	14%	9%	3%	3%	2%	9%	3%	7%	16%	2%	5%	2%	2%	3%	2%	5%	2%	2%	2%	2%	3%	2%	5%	2%	2%	2%	2%	3%

Table 1. Listing of oral findings in the published literature. Note: The findings in this case report listed on the last line.

hydrolethalus syndrome[5,13,15,33,40]; Fryns anophthalmia syndrome[40]; Delleman syndrome[40]; holoprosencephaly/polydactyly syndrome[23]; craniofrontodysplasia[21,37]; acrofrontofacionasal syndrome associated with genitourinary anomalies[21]; trisomy 13[20]; tetrasomy 12p[19]; congenital hypothalamic hamartoblastoma syndrome[37]; W syndrome[37]; syndrome of micromelia, polysyndactyly, multiple malformations, and fragile bones[37]; hypertelorism with holoprosencephaly and ectrodactyly[37]; Mohr syndrome[13]; and acromelic frontonasal dysplasia.[48] A careful review of the signs and symptoms of each of these disorders can aid in ruling out these possible diagnoses.

This differential diagnosis list is consistent with ACS' classification as an MCA/MR disorder, and a wide variety of developmental defects can possibly be found in individual patients. Referral to a genetic counselor is indicated to discuss with the parents the risk of this disorder occurring in subsequent siblings.

Our patient displayed several of the frequently reported findings of previous authors, including cleft lip/palate, high-arched palate, long philtrum, and an open mouth posture at rest. Not reported in other articles but one related to the patient described by Shilpa[6] are over-retained primary teeth. Since tooth eruption is a complex biological process involving numerous signaling chemicals, cytokines, and putative eruption genes located in the dental follicle and stellate reticulum, genetic disorder patients have a higher incidence of delayed or arrested eruption than do healthy patients.[54] The relationship between ACS' genetic basis and its relationship to any of the genes and chemicals required for tooth eruption is fertile ground for future research.

The over-retained/unerupted teeth may also be related to gingival enlargement secondary to anti-seizure medications. Both patients were receiving medications for a seizure disorder. Gingival overgrowth occurs much more frequently with phenytoin. Gingival overgrowth, however, has been linked to the administration of valproic acid[52,53] and drug-induced gingival overgrowth has been associated with the delayed eruption of teeth.[44,45] Most often this delay is assigned to the increased density of the gingival tissues, but a definitive reason has not been established. In our case, there has been limited resorption of bone over the unerupted permanent molars and limited resorption on the roots of the primary mandibular incisors. None of the previous case reports have suggested bone remodeling defects or osteoclast/dentinoclast defects which may influence the resorption of the overlying alveolar bone. There is no reported history of any bone remodeling or osteoclast/dentinoclast defects in our patient. The use of bisphosphonates has also been linked to a delay in tooth eruption in rats,[55] but there were no reports of the patient receiving any bisphosphonate medications, which have an apoptotic effect on osteoclasts.

The treatment option of extracting primary teeth to prompt the eruption of permanent successors can reasonably be debated. The importance of discussing the potential risks (continued uneruption of the permanent teeth despite the removal of the primary teeth) and benefits (possible acceleration of the eruption process) of any treatment options are vital to the informed consent process. The recommendation to remove the teeth was based on the orthodontic literature demonstrating accelerated eruption of the permanent tooth with extraction of the primary tooth when at least two thirds of the permanent tooth root had developed.[56,57] The prognosis of this treatment was estimated as good. Removal of the primary mandibular incisors in our case did result in the eventual eruption of 2 permanent mandibular incisors during the recall period.

Treating patients with special health care needs involves having thorough background knowledge of the patient's condition in conjunction with expert clinical skills. There are many genetic syndromes still to be identified as the science in genomics continues to evolve and improve. The ability of modern medicine to provide longer life spans and higher qualities of life for patients who previously would not have survived their disease increases the demands on health care providers to be knowledgeable in many more uncommon syndromes.

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