Dental and Maxillofacial Signs in Aarskog Syndrome: A Review of 3 Siblings and the Literature

Arnaud Depeyre, MD, * *Matthias Schlund, MD,* † *Rémi Gryseleyn, MD,* ‡ *and Joël Ferri, MD, PhD* §

Purpose: Dagfinn Aarksog first described faciodigitogenital syndrome in 1970. Its inheritance is X linked and autosomally recessive. Currently, the diagnosis of Aarskog-Scott syndrome (ASS) is based on clinical dysmorphologic findings and can be supported by genetic examination.

Report of Cases: This report describes 3 brothers already diagnosed with ASS who were referred for examination of oral and maxillofacial malformations associated with ASS. They presented classic features of ASS, such as digital and genital (shawl scrotum) anomalies. More specifically, in terms of orbitopalpebral malformations, they showed marked ptosis with hypertelorism and antimongoloid palpebral fissure that gave them the characteristic facies. Concerning their oral and maxillofacial malformations, they had dental and skeletal major discrepancies and some dental agenesia.

Discussion and Conclusion: ASS is a rare X-linked syndrome composed of numerous morphologic facial, digital, and genital anomalies. The diagnosis is established genetically with the FGD1 mutation but there is no phenotypic and genotypic correlation with FGD1 mutations. Concerning maxillofacial malformations, maxillary and mandibular hypoplasia with jaw discrepancies can be found, as can teeth anomalies. It seems that these anomalies are widely underestimated.

J Oral Maxillofac Surg 76:2202-2208, 2018

Dagfinn Aarskog[1] first described faciodigitogenital syndrome or faciogenital dysplasia in 1970. The following year, Charles I. Scott[2] described a similar case, hence the name Aarskog-Scott syndrome (ASS). It is a genetically and clinically variable disease associated with X-linked, autosomal recessive, and autosomal dominant inheritance. The FGD1 gene mutation, located on Xp11.21, is responsible for ASS.[3,4] It is a relatively rare disorder, with an estimated population prevalence equal to or slightly lower than 1 in 25,000. ASS shows a male predominance and is characterized by short stature and facial, hand, and foot skeletal and genital abnormalities.[5]

Subsequent to these initial publications, few case reports have been published in the literature detailing the systemic features associated with this syndrome.[6-8] Even less has been presented concerning the associated dental and maxillomandibular consequences. This is the first report of 3 siblings with confirmed FGD1 mutation for ASS, in whom the

*Resident, Oral and Maxillofacial Department, Estaing Hospital, CHU Clermont-Ferrand, Clermont-Ferrand; Faculty of Medicine, Université d'Auvergne, Clermont-Ferrand; Laboratoire CROC EA 3847, Faculty of Dental Surgery, Université d'Auvergne, Clermont-Ferrand; Inserm U1008, Controlled Drug Delivery Systems and Biomaterials, Lille, France.

†Resident, Inserm U1008, Controlled Drug Delivery Systems and Biomaterials, Lille; Université Lille 2 Droit et Santé, Lille; Oral and Maxillofacial Department, Roger Salengro Hospital, Lille, France.

‡Resident and Private Practitioner, Université Lille 2 Droit et Santé, Lille; Oral and Maxillofacial Department, Roger Salengro Hospital, Lille, France.

§Professor and Department Head, Inserm U1008, Controlled Drug Delivery Systems and Biomaterials, Lille; Université Lille 2 Droit et Santé, Lille; Oral and Maxillofacial Department, Roger Salengro Hospital, Lille, France.

Conflict of Interest Disclosures: None of the authors have a relevant financial relationship(s) with a commercial interest.

Address correspondence and reprint requests to Dr Depeyre: CHU Clermont-Ferrand, Service de Chirurgie Maxillo-Faciale et Stomatologie, 1 Place Lucie Aubrac, 63003 Clermont-Ferrand Cedex 1, France; e-mail: depeyrearnaud@gmail.fr

Received February 19 2018
Accepted March 21 2018

0278-2391/18/30285-4
https://doi.org/10.1016/j.joms.2018.03.027

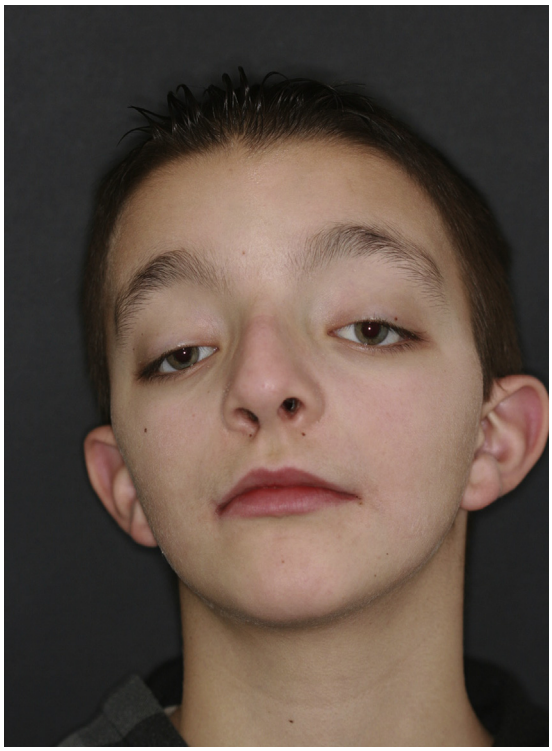

FIGURE 1. Facial photograph of the oldest brother (case 1) showing typical craniofacial signs of Aarskog-Scott syndrome.

Depeyre et al. Dento-Maxillofacial Signs in Aarskog Syndrome. J Oral Maxillofac Surg 2018.

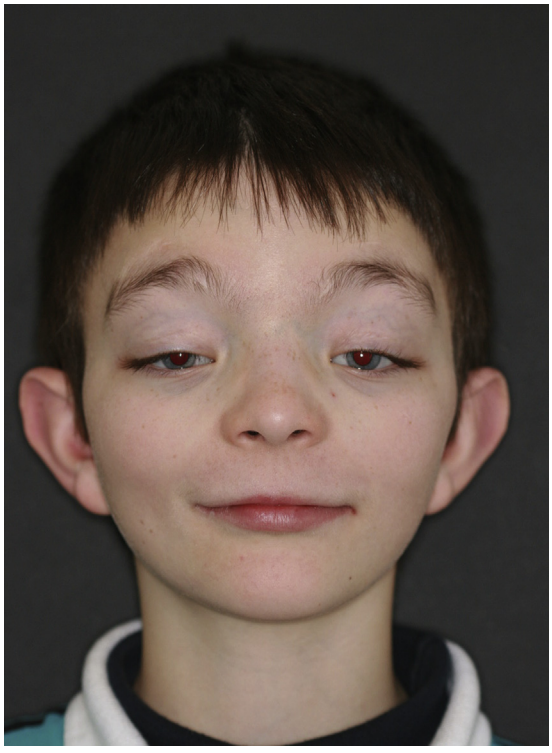

FIGURE 2. Facial photograph of the second brother (case 2) showing typical craniofacial signs of Aarskog-Scott syndrome.

Depeyre et al. Dento-Maxillofacial Signs in Aarskog Syndrome. J Oral Maxillofac Surg 2018.

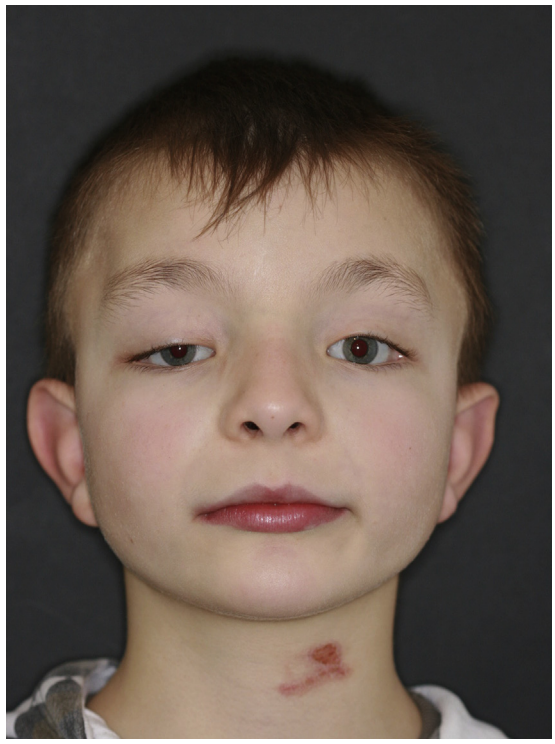

FIGURE 3. Facial photograph of the youngest brother (case 3) showing typical craniofacial signs of Aarskog-Scott syndrome.

Depeyre et al. Dento-Maxillofacial Signs in Aarskog Syndrome. J Oral Maxillofac Surg 2018.

oral and maxillofacial malformations related to this disorder were identified and treated.

Report of Cases

Three brothers, 9, 11, and 14 years old, were referred for screening of oral and maxillofacial

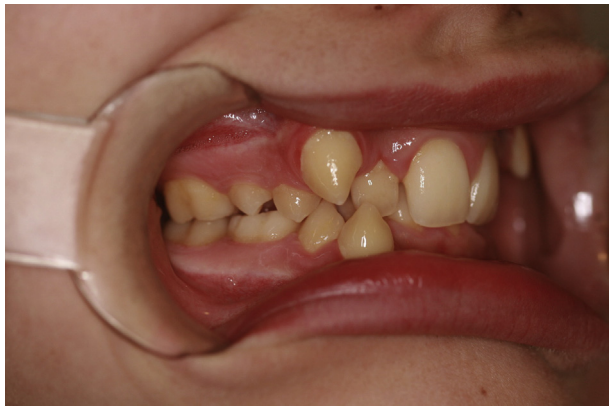

FIGURE 4. Dental occlusion image showing dental abnormalities and jaw discrepancy in case 1. Note buccally and inferiorly positioned maxillary canine teeth and delayed eruption of the maxillary left second premolar.

Depeyre et al. Dento-Maxillofacial Signs in Aarskog Syndrome. J Oral Maxillofac Surg 2018.

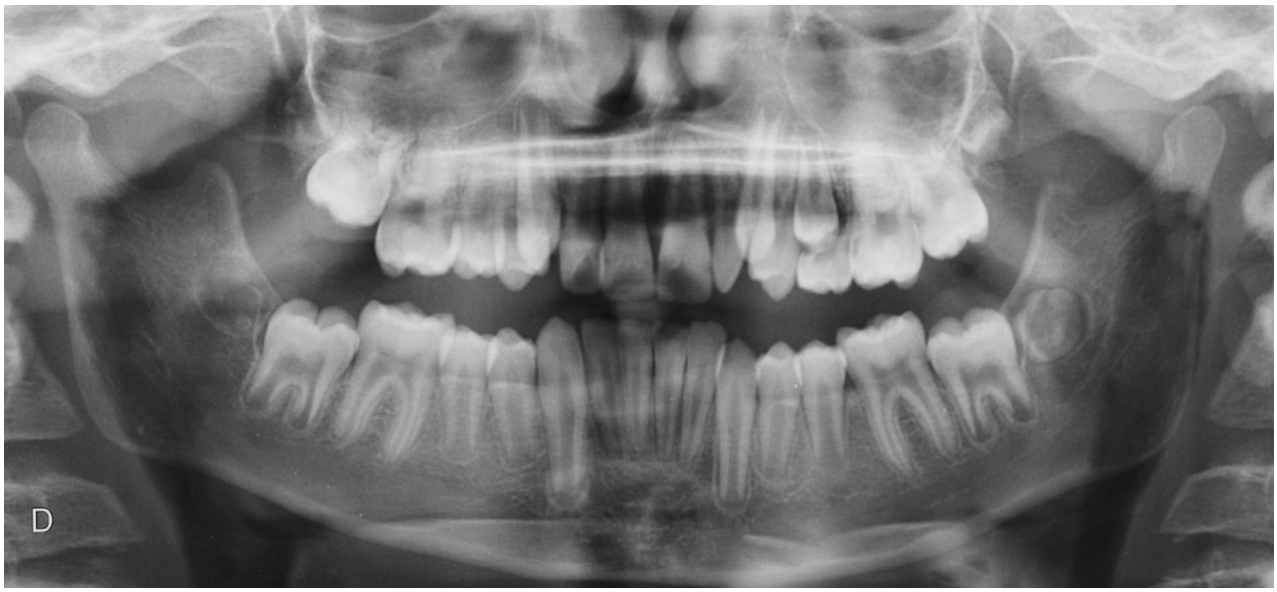

FIGURE 5. Orthopantomogram of case 1. Note delayed eruption of maxillary left second premolar.

Depeyre et al. Dento-Maxillofacial Signs in Aarskog Syndrome. J Oral Maxillofac Surg 2018.

malformations as part of ASS to the Department of Oral and Maxillofacial Surgery at the University Hospital of Lille (Lille, France). They were full-term infants previously diagnosed with ASS owing to congenital and specific facial features consistent with this syndrome. Positive findings for the FGD1 mutation had been confirmed for each brother. These were the only known cases in the family. There was no known consanguinity in the family. Their sister did not show any malformations.

The first consultation concerned the oldest brother and was motivated by problems with dentofacial orthopedics and, more particularly, for a typical transverse maxillary hypoplasia. The orthodontist wondered whether surgery was necessary. The facial aspect of this patient was suggestive and genetic investigation of the patient and his siblings was queried. The 2 younger brothers were seen next and cared for surgically.

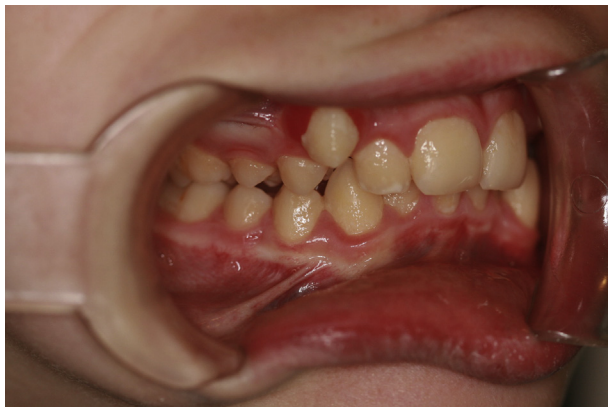

FIGURE 6. Dental occlusion image showing dental abnormalities and jaw discrepancy in case 2. Note buccally and inferiorly positioned maxillary canine teeth and delayed eruption of the second mandibular premolar teeth.

Depeyre et al. Dento-Maxillofacial Signs in Aarskog Syndrome. J Oral Maxillofac Surg 2018.

The 3 siblings presented short stature for their age and the oldest brother had delayed puberty. Each boy had numerous morphologic and developmental anomalies. The authors observed their particular global facial morphology; the most remarkable anomaly concerned the orbitopalpebral region with marked uni- or bilateral ptosis associated with hypertelorism and antimongoloid palpebral fissure (Figs 1-3). The extraoral examination also showed a hypoplastic midface with decreased facial height, a stubby nose and anteverted nostrils, a long philtrum, thin lips with an everted lower lip, and prominent low-set ears.

The intraoral examination showed that the 3 patients had hypoplastic jaws with dental and skeletal Class II malocclusion. The oldest brother had severe arch length discrepancy, with the maxillary canines buccally and inferiorly positioned, associated with delayed eruption of the maxillary left second premolar (Figs 4 and 5). The upper canines and premolars exhibited a very conical shape. The second brother also showed a Class II dysmorphia with a mild arch length discrepancy and buccally and inferiorly positioned maxillary canines. The authors also noted delayed eruption of the second mandibular premolar teeth, an agenesis of the left upper and lower third molars, and a dystrophic right upper third molar (Figs 6 and 7). The youngest brother had Class II dysmorphia

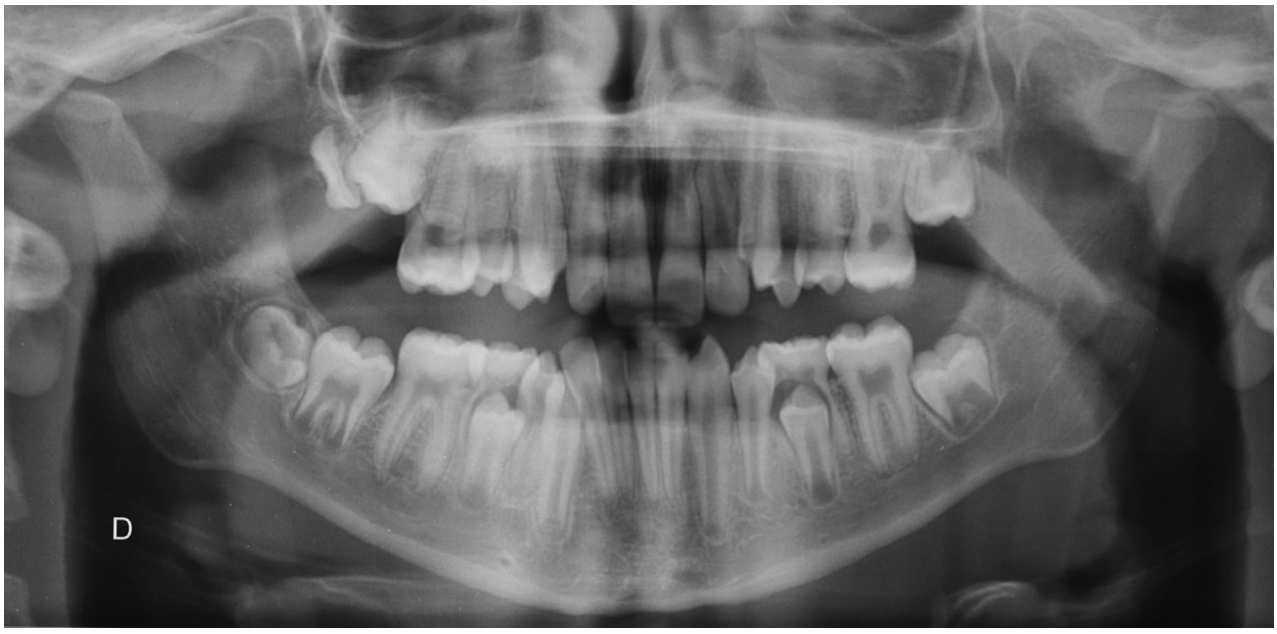

FIGURE 7. Orthopantomogram of case 2. Note agenesis of the left upper and lower third molars and a dystrophic right upper third molar.

Depeyre et al. Dento-Maxillofacial Signs in Aarskog Syndrome. J Oral Maxillofac Surg 2018.

and a marked vertical overbite with the lower incisors in contact with the anterior palatal region. Agenesis of the upper right lateral incisor and right coronoid process dysplasia also were observed (Figs 8 and 9).

In each patient, the extrafacial examination showed brachydactyly, joint hyperlaxity, and a single transverse palmar crease or "simian crease" (Figs 10 and 11). With respect to the genital malformation, they had a shawl scrotum represented by an upper scrotal skin rising over the base of the penis. Their cardiovascular system was entirely normal.

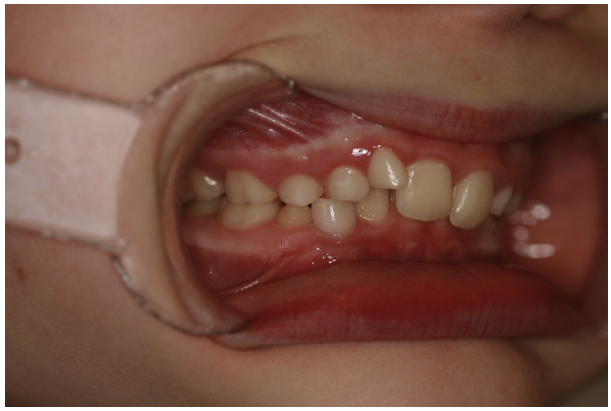

FIGURE 8. Dental occlusion image showing dental abnormalities and jaw discrepancy in case 3. Note marked vertical overbite and agenesis of the upper right lateral incisor.

Depeyre et al. Dento-Maxillofacial Signs in Aarskog Syndrome. J Oral Maxillofac Surg 2018.

Discussion

ASS affecting 3 siblings and presenting with almost the same dental and maxillofacial features is a rare observation and the first reported cases in the international literature. These 3 brothers had characteristic facial, genital, and extremity malformations. Each presented with a remarkably similar maxillomandibular discrepancy associated with multiple dental anomalies, which led them to visit an oral and maxillofacial surgery department.

Currently, the diagnosis of ASS is based on clinical dysmorphologic findings and can be supported by genetic testing. To date, approximatively 30 different mutations have been reported, with no relation found between the severity of the disease and the type of mutation.[9] The inheritance of ASS is X linked and typically autosomally recessive, although autosomal dominant inheritance has been described.[3,10] The FGD1 gene mutation is responsible for ASS; this gene plays a role in the signaling pathways of cytoskeleton organization and embryonic morphogenesis. There is no phenotypic and genotypic correlation with FGD1 mutations in patients with ASS, which could explain why these 3 siblings presented with similar features but variable expressions of the disorder.[3,5,11-13] In other words, with the same FGD1 mutation, the 3 siblings exhibited variability in the severity of their manifestation of ASS. This heterogeneity of clinical presentation can make the diagnosis of ASS difficult because it shares phenotypic similarities with Robinow and Noonan syndromes.[9,14]

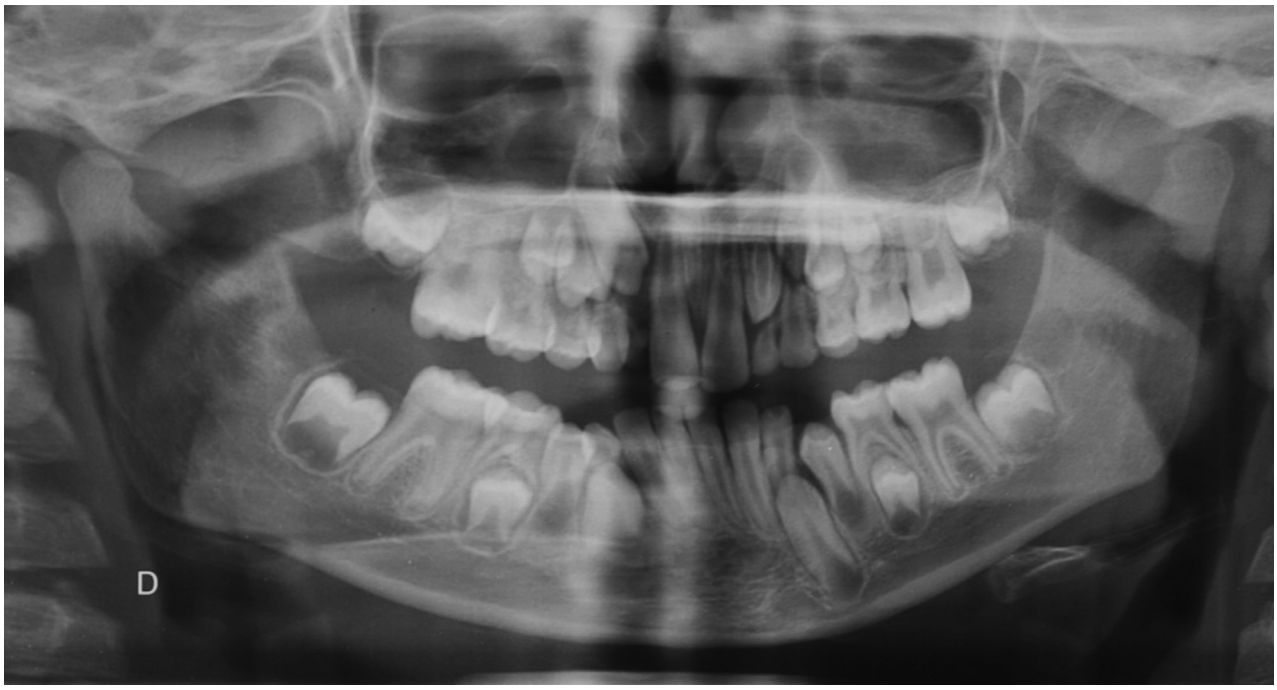

FIGURE 9. Orthopantomogram of case 3. Note agenesis of the upper right lateral incisor and right coronoid process dysplasia.

Depeyre et al. Dento-Maxillofacial Signs in Aarskog Syndrome. J Oral Maxillofac Surg 2018.

Patients with ASS can present with several systemic (genital, hands, feet, skeletal, craniofacial, and others) manifestations. Short stature, shawl scrotum, cryptorchidism, macroorchidism, hypospadias, inguinal hernia, syndactyly, brachydactyly, interdigital webbing, hyperextensible joints, single palmar creases, limited thumb abduction, metatarsus adductus, camptodactyly, lymphedema, cervical spine abnormalities, spina bifida occulta, scoliosis, and pectus excavatum are the most common clinical signs associated with the craniofacial features of ASS. Some psychodevelopmental disorders have been reported, such as autism, mild developmental delay, and behavioral and personality disorders.[5,15,16] Myopathy and distal arthropathy have been reported in ASS,[12] as have brain

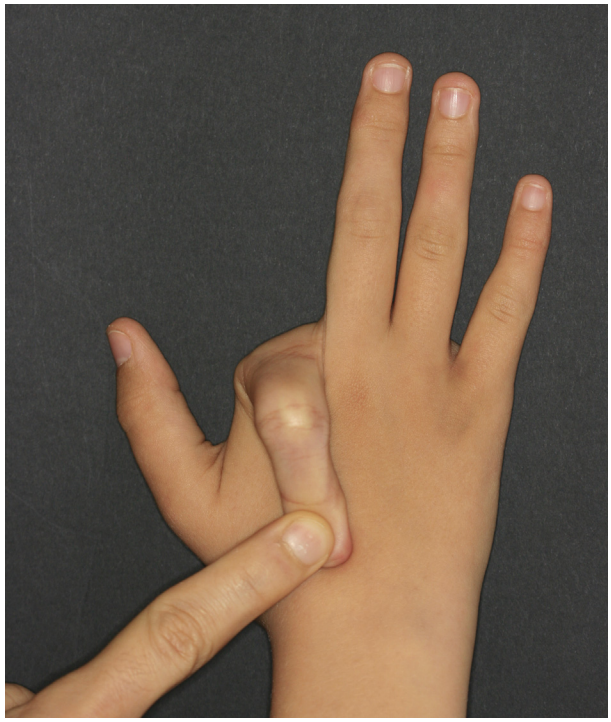

FIGURE 10. Image of joint hyperlaxity in the oldest brother (case 1).

Depeyre et al. Dento-Maxillofacial Signs in Aarskog Syndrome. J Oral Maxillofac Surg 2018.

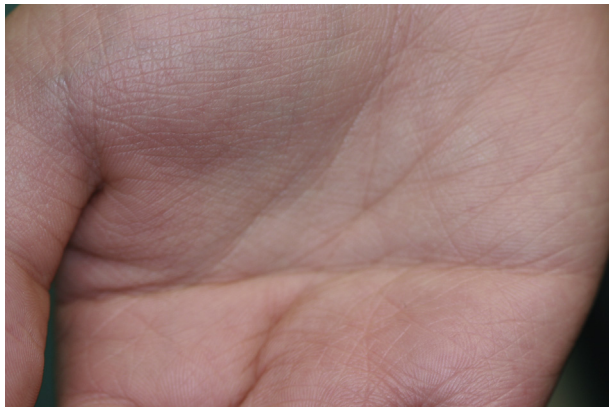

FIGURE 11. Image of single transverse palmar crease "simian crease" in the youngest brother (case 3).

Depeyre et al. Dento-Maxillofacial Signs in Aarskog Syndrome. J Oral Maxillofac Surg 2018.

Table 1. MAXILLOFACIAL AND DENTAL FEATURES ASSOCIATED WITH ASS REPORTED IN THE LITERATURE

Year of Publication	Study	Type of Article	Dental and Maxillofacial Findings Associated With AAS
1976	Melnick and Shields	case report	shortened cephalometric cranial base and maxilla; maxillary hypoplasia; "col" deformity of anterior mandible (hypertrophic mental tubercles); dental hypoplasia; enamel dysplasia
1979	Halse et al	case series (10 patients)	orthodontic anomalies with jaw discrepancies; retarded development and eruption of permanent teeth; hypodontia
1990	Dayal et al	case report	hypoplastic jaws; delayed eruption of permanent teeth; agenesia of multiple teeth
1999	Reddy et al	case report	increased total anterior facial and lower anterior facial height; Class I skeletal pattern; hypoplastic retruded maxilla and mandible
2012	Closs et al	case report	decreased facial height owing to hypoplastic midface; maxillary and mandibular dentoalveolar discrepancy; deep bite; early loss of primary teeth; delayed eruption of permanent teeth
2016	Ahmed et al	case report	decreased vertical facial height; maxillary hypoplasia; missing teeth

Abbreviation: ASS, Aarskog-Scott syndrome.

Depeyre et al. Dento-Maxillofacial Signs in Aarskog Syndrome. J Oral Maxillofac Surg 2018.

and heart malformations.[17,18] The craniofacial features include round face, maxillary hypoplasia, widow's peak, frontal bossing, low-set ears, fleshy earlobes, hypertelorism, ptosis, downward-slanting palpebral fissures, hyperopia, strabismus, broad nasal bridge, small or short nose, anteverted nostrils, wide philtrum, curved linear dimple below the lower lip, cleft lip and palate, and short neck.[6,9]

These 3 patients presented maxillomandibular discrepancies with characteristic Class II skeletal patterns associated with some dental abnormalities. The occlusion and dental anomalies related to the oral and maxillofacial features of ASS have rarely been described. There are very few publications concerning these findings. A literature review was performed in PubMed using *dental*, *maxillofacial*, and *Aarskog syndrome* as keywords. Findings are presented in Table 1. Decreased facial height associated with hypoplastic jaws is always cited.[8,19,20] A dentoalveolar discrepancy from a loss of space in the maxillary and mandibular arches is common.[7,21] By contrast, Reddy et al[22] reported a case of increased total facial height, especially of the lower third of the face, associated with a hypoplastic retruded maxilla and mandible. The increased facial height can be explicated by marked hypoplasia of the mandible with an extreme open mandibular angle. Concerning dental features associated with ASS, multiple agenesia, hypoplasia, and delayed eruption of permanent teeth are reported. Melnick and Shields[19] also reported dental dyschromia in relation to enamel dysplasia.

Given the effect of ASS on facial growth and dental and maxillary development, there is reason to believe that those dental and maxillofacial symptoms are widely underdiagnosed, with these patients being insufficiently referred to an oral and maxillofacial surgery department.[22] The interest of the maxillofacial surgeon in the recognition of the syndrome concerns the occlusal anomalies requiring early attention and surgical treatment. There are clinical benefits from

early diagnosis for surgical and orthodontic treatments, facial growth, dental eruption, and feeding or speech functions.

ASS is a rare X-linked genetic syndrome with variable phenotypic presentation. It was well described in the first publication in 1970. However, malocclusion characterized by hypoplastic jaw discrepancy and teeth anomalies seems to be underestimated and, as a consequence, inadequately evaluated and managed.

References

1. Aarskog D: A familial syndrome of short stature associated with facial dysplasia and genital anomalies. J Pediatr 77:856, 1970
2. Scott CI: Unusual facies, joint hypermobility, genital anomaly and short stature: A new dysmorphic syndrome. Birth Defects Orig Artic Ser 7:240, 1971
3. Pasteris NG, Cadle A, Logie LJ, et al: Isolation and characterization of the faciogenital dysplasia (Aarskog-Scott syndrome) gene: A putative Rho/Rac guanine nucleotide exchange factor. Cell 79:669, 1994
4. Pasteris NG, Buckler J, Cadle AB, et al: Genomic organization of the faciogenital dysplasia (FGD1; Aarskog syndrome) gene. Genomics 43:390, 1997
5. Orrico A, Galli L, Clayton-Smith J, et al: Clinical utility gene card for: Aarskog-Scott syndrome (faciogenital dysplasia)—Update 2015. Eur J Hum Genet 23, 2015
6. Taub MB, Stanton A: Aarskog syndrome: A case report and literature review. Optometry 79:371, 2008
7. Closs LQ, Tovo M, Dias C, et al: Aarskog-Scott syndrome: A review and case report. Int J Clin Pediatr Dent 5:209, 2012
8. Ahmed A, Mufeed A, Ramachamparambathu AK, et al: Identifying Aarskog syndrome. J Clin Diagn Res 10:ZD09, 2016
9. Altıncık A, Kaname T, Demir K, et al: A novel mutation in a mother and a son with Aarskog-Scott syndrome. J Pediatr Endocrinol Metab 26:385, 2013
10. Grier RE, Farrington FH, Kendig R, et al: Autosomal dominant inheritance of the Aarskog syndrome. Am J Med Genet 15:39, 1983
11. Moraes SG, Guerra-Junior G, Maciel-Guerra AT: Female counterpart of shawl scrotum in Aarskog-Scott syndrome. Int Braz J Urol 32:459, 2006
12. Al-Semari A, Wakil SM, Al-Muhaizea MA, et al: Novel FGD1 mutation underlying Aarskog-Scott syndrome with myopathy and distal arthropathy. Clin Dysmorphol 22:13, 2013
13. Parıltay E, Hazan F, Ataman E, et al: A novel splice site mutation of FGD1 gene in an Aarskog-Scott syndrome patient with a large anterior fontanel. J Pediatr Endocrinol Metab 29:1111, 2016
14. Orrico A, Galli L, Clayton-Smith J, et al: Clinical utility gene card for: Aarskog-Scott syndrome (faciogenital dysplasia). Eur J Hum Genet 19, 2011
15. Assumpcao F, Santos RC, Rosario M, et al: Brief report: Autism and Aarskog syndrome. J Autism Dev Disord 29:179, 1999
16. Orrico A, Galli L, Buoni S, et al: Attention-deficit/hyperactivity disorder (ADHD) and variable clinical expression of Aarskog-Scott syndrome due to a novel FGD1 gene mutation (R408Q). Am J Med Genet A 135:99, 2005
17. Fernandez I, Tsukahara M, Mito H, et al: Congenital heart defects in Aarskog syndrome. Am J Med Genet 50:318, 1994
18. Diluna ML, Amankulor NM, Johnson MH, et al: Cerebrovascular disease associated with Aarskog-Scott syndrome. Neuroradiology 49:457, 2007
19. Melnick M, Shields ED: Aarskog syndrome: New oral-facial findings. Clin Genet 9:20, 1976
20. Dayal PK, Chaudhary AR, Desai KI, et al: Aarskog syndrome: A case report. Oral Surg Oral Med Oral Pathol 69:403, 1990
21. Halse A, Bjorvatn K, Aarskog D: Dental findings in patients with Aarskog syndrome. Scand J Dent Res 87:253, 1979
22. Reddy P, Kharbanda OP, Kabra M, et al: Dental and craniofacial features of Aarskog syndrome: Report of a case and review of literature. J Clin Pediatr Dent 23:155, 1999