CASE REPORTS

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Oral manifestations of Noonan syndrome: review of the literature and a report of four cases

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Abstract

Noonan syndrome (NS) was described by Noonan and Ehmke as a multi-system disorder, which is typically evident at birth. The incidence of this syndrome is estimated to be one per 2500 to one per 1000 and affects both genders. While the clinical manifestations of NS have been well documented, the oral manifestations have not been extensively discussed. The purpose of the present article is to (*a*) review the oral manifestations of NS reported in the literature, and (*b*) describe four cases (three females and one male) of NS, who presented with short stature, cardiac problems and various oral findings. Based on these cases, we conclude that many oral anomalies may have possible relationships with NS, which require multidisciplinary treatment planning and timely management. The importance of oral findings in NS has largely gone unnoticed and it is essential to consider oral manifestations as scoring criteria in the diagnosis of NS.

Keywords: oral manifestations, Noonan syndrome, southern Chinese.

Introduction

Noonan syndrome (NS) [http://omim.org/entry/163950] is an autosomal dominant disorder with an estimated incidence of between one in 1000 and one in 2500 live births [1]. The characteristic findings of this syndrome include short stature, distinctive facial features, chest deformity, and congenital heart disease [2]. These findings were original reported by Kobylinski [3], and first documented by Noonan and Ehmke [4] as a unique entity with unusual facies and multiple malformations, and congenital heart defects. Subsequently, Noonan [5] described atypical facies, congenital heart disease, and clinical features of Turner syndrome with normal chromosomes in 19 cases (12 males and seven females). These two articles caused puzzlement over the terminology surrounding an individual with a phenotype of Turner syndrome. Meanwhile, Ford *et al.* [6] had identified the karyotype 45X in a patient with the diagnosis of Turner syndrome. Consequently, a clear division was subsequently made between Turner syndrome (45X, female only) and NS. The substantial differences between the two syndromes are now well documented. Although the basic features of NS resemble those of Turner syndrome, the latter syndrome only affects females. Subsequently, "male Turner syndrome" was the term used to describe NS. Noonan syndrome also became known as "pseudo-Ullrich Turner syndrome", "Turner like syndrome more details", "female pseudo-Turner syndrome" and "webbed neck syndrome".

Noonan syndrome frequently presents with an autosomal dominant pattern of inheritance, with a high proportion of maternal transmission [7–9]. It has been reported that the PTPN11 mutations in sporadic NS patients are primarily of paternal origin [10, 11]. Pharmacological doses of growth hormone can be used to hasten growth during the early years of life of children with NS. Earlier reports demonstrated the long-term benefits of this treatment protocol [12]. Noonan syndrome patients with a mutation in the PTPN11 gene usually respond less effectively to growth hormone than those without the PTPN11 mutation [13].

Frequently, the diagnosis of NS is based on facial and musculoskeletal features. In infancy, the facial appearance is characteristic and becomes more subtle towards middle childhood and adulthood [14]. Infants with NS usually presents with a small face which appears to be tucked beneath a large cranium, the head is large with narrowing at the temples, these features result in a tall forehead. There is hypotelorism and the nose is short; while the ears are low-set, posteriorly rotated and an oval in shape. The neck is also short with a low posterior hairline. Towards late childhood, the expressionless facial appearance resembles that of a myopathic face. In adolescence, the face is more triangular with a wide forehead, and pointed chin. The eyes are less prominent but have sharp features. The neck is longer than normal, and skin webbing or trapezius muscle prominence (webbed neck) are characteristic features of NS. Also, the nipples are wide-spaced and low-set. Rounded shoulders and hyperextensibility are common features in subjects with NS [15]. Scoliosis has been reported in 10% to 15% of NS patients [16]. There are several disorders with significant phenotypic overlaps with NS; such as Turner syndrome, cardiofaciocutaneous (CFC) syndrome, Costello syndrome, Leopard syndrome, Aarskog syndrome and Baraitser–Winter syndrome [2]; because of the differences in treatment, the prognosis, and recurrence concerns, the accurate early diagnosis of NS is critical.

Noonan syndrome, which is characterized by ocular, facial, cardiac, and oral anomalies, is association with short stature. It has been suggested that early diagnosis of NS is

important, because of its association with general and oral health [2]. However, the oral manifestations have never been extensively discussed in the literature. Therefore, the purpose of this article was to review the oral manifestations of the Noonan syndrome and to present a report of the oral manifestations in four southern Chinese subjects.

Review of the literature

Materials and Methods

A narrative review was performed on the oral manifestations of NS. This review differs from a systematic review by involving a general discussion of the subject, whilst not having a stated hypothesis. An extensive search of the reported literature, published between January 1966 and May 2012 was conducted using the MEDLINE, Embase, and PubMed databases. The key words used in the search strategy were "oral manifestations", "dental manifestations", and "Noonan syndrome" in various combinations. The citation lists from the identified references were subsequently examined and a hand search was also performed in an attempt to identify additional reports.

Results

The literature search yielded case reports and a few case studies that reported the oral manifestations of NS. The common oral manifestations included micrognathia, high arch palate, malocclusion, impacted teeth, retroclined mandibular incisors and giant cells in the jaws. The case reports and studies of the oral manifestations present in patients with NS are summarized in Table 1 [17–39].

Table 1 – ***Published reports on the oral manifestations of Noonan syndrome***

Authors	Cases (gender)	Age [years]	Oral manifestations
Baird and De Jong [17]	7	-	Anomalous upper lateral incisors
Nelson *et al.* [18]	1 (F)	6	Exanthemas eyes high arch palate
Chuong *et al.* [19]	2 of 17	-	Central giant cell lesions of jaw
Dunlap *et al.* [20]	Case 1 (M)	5.1	Cherubism
	Case 2 (M)	13.1	
	Case 3 (M)	6.9	
	Case 4 (M)	8	
Cohen and Gorlin [21]	14	-	Giant cell lesions of bones, and/or soft tissues
Torres-Carmona *et al.* [22]	2 (F)	-	Periodontitis
Sugar *et al.* [23]	1 (M)	22	Anterior open bite, prognathic mandible, malocclusion
Lucker and Steijlen [24]	1(M)	-	Leucokeratosis of the lips and gingival
Addante and Breen [25]	1 (M)	4	Cherubism
Nirmal *et al.* [26]	1 (M)	4.5	High arch palate
Barberia Leache *et al.* [27]	Case 1 (F)	4.3	Severe caries, radicular anomalies of primary molars
	Case 2 (M)	4.1	Severe caries, malocclusion, anterior open-bite
	Case 3 (M)	9.3	Severe caries, malocclusion, eruption cyst
Okada *et al.* [28]	1 (M)	8.1	High arch palate, micrognathic mandible, posterior cross bite, anterior open-bite, early exfoliation of canines
Yazdizadeh *et al.* [29]	1 (M)	22	Neurofibromatosis and central giant cell granuloma
Edwards *et al.* [30]	1 (F)	8	Bilaterally occurring central giant cell lesions
Asokan *et al.* [31]	Case 1 (F)	13	High arch palate, anterior open bite, hypoplastic jaws, retrognathic maxilla, prognathic mandible
Cancino *et al.* [32]	1 (F)	14	Multiple giant cell lesions in the mandible
Sharma *et al.* [33]	1 (F)	9	Malocclusion, crowding, marginal gingivitis
Ortega Ade *et al.* [34]	Case 1 (M)	14	Malocclusion, labial hypotonia, gingival inflammation, retrognathic maxilla and mandible, proclined incisors in maxilla and mandible
	Case 2 (M)	13	Malocclusion, gingival inflammation, supernumerary teeth, prognathic maxilla and mandible, retroclined mandibular incisors
Sahebjamee *et al.* [35]	1 (F)	19	Gingival enlargement, crowding associated with midline diastema, malocclusion, anterior cross-bite, taurodontism, impacted teeth, idiopathic osteosclerosis, hypodontia
Emral and Akcam [36]	1 (F)	13.3	Malocclusion, hypodontia, high arch palate, impacted teeth deep-bite, retroclined mandibular incisors, asymmetry of tooth morphology of maxillary first molars
Ierardo *et al.* [37]	1 (F)	8	Malocclusion, deep bite, ectopic eruption, hypodontia
Bufalino *et al.* [38]	1 (M)	8	Giant cell lesions
Toureno and Park [39]	1 (M)	14.8	Severe gingivitis and supernumerary teeth, bilateral enlargement of the mental foramens and inferior-alveolar canals

M: Male; F: Female.

Baird and De Jong [17] were the first to document seven cases spanning three generations with anomalous maxillary lateral incisors. Chuong *et al.* [19] subsequently reported central giant cell lesions the jaws of two out of 17 patients with NS; while Cohen and Gorlin [21] reported 14 cases with similar findings. The association of periodontitis with NS was addressed in two patients reported by Torres-Carmona *et al.* [22]. Subsequently, several authors have discussed a number of oral manifestations such as high arch palate [18], severe dental caries, radicular anomalies of primary molar, malocclusion, anterior open-bite, eruption cysts [27], micrognathic mandible, posterior cross-bite, early exfoliation of primary canines [28], hypoplastic jaws, retrognathic maxilla and prognathic mandible [31], labial hypotonia, gingival inflammation, proclined incisors, supernumerary teeth [34], gingival enlargement, crowding associated with a midline diastema, taurodontism, idiopathic osteosclerosis, hypodontia [35], deep-bite, asymmetry of tooth morphology of maxillary first molars

[36]. More recently, Toureno and Park [39] reported a case with supernumerary teeth and bilateral enlargement of the mental foramen.

Case Reports

The four southern Chinese subjects (one boy and three girls) with NS in the present study were referred for the management of dental caries. These four cases exhibit the typical features of NS, such as short stature, cardiac problems, plus eye and ear abnormalities. These patients all had mild to severe intellectual disabilities. They have been regularly reviewed at six-month intervals for three years and were still currently attending for reviews.

Case No. 1

A nine years eight months old Chinese boy, who was the fourth child of a healthy non-consanguineous Chinese couple, was diagnosed with NS. The boy was born full-term by vaginal delivery. His birth weight was 3.2 kg and his height was 45 cm. His medical history revealed a congenital heart defect and epilepsy. He underwent eye and lip surgeries at the ages of 3- and 5-year-old, respectively. His past dental history revealed that he had received multiple restorations. Examination of the parents of the propositi and his two elder sister revealed that they were unaffected by the syndrome. However, his elder brother had been diagnosed with odontodwarphomorphism. Extra-orally, the boy presented with the characteristic features of triangular faces with a concave profile and webbed neck, ptosis, hypertelorism, flat base of the nose, low-setting ears, fixed facial expression, and low posterior hairline. The intra-oral examination revealed a permanent dentition with poor oral hygiene and generalized gingival inflammation. He brushed his teeth once daily and had never used dental floss. The maxillary arch was parabolic; while the mandibular arch was U-shaped (Figure 1).

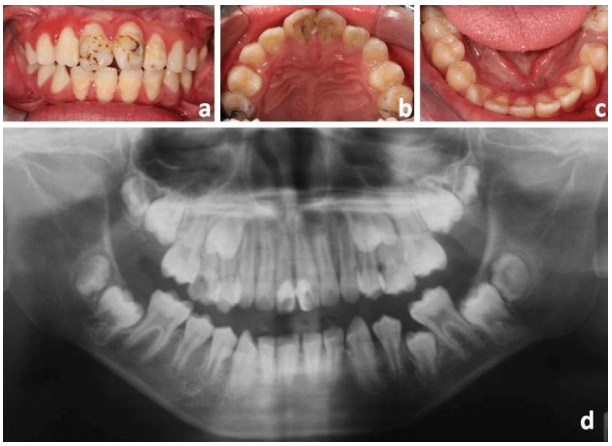

Figure 1 – *Case No. 1: (a) frontal view of the maxillary and mandibular arches, (b) occlusal view of maxillary arch, (c) occlusal view of mandibular arch, and (d) panoramic radiograph revealing the impaction of teeth 15, 25, 35 and taurodontism of the maxillary first permanent molars.*

Clinical examination revealed an Angle's class I malocclusion with mild crowding in the maxillary and mandibular arches, generalized macrodontia, hypoplastic areas on the maxillary central incisors, high arched palate, teeth 15, 25, and 35 were missing and the incisors were proclined. Radiographic examination revealed impaction of teeth 15, 25 and 35, also there was taurodontism of the maxillary first permanent molars (Figure 1).

His weight and height were found to be 26.5 kg (between 25th and 50th percentile) and 128 cm (below the 25th percentile) respectively. He is presently under regular review pending future management.

Case No. 2

A 12 years eight months old Chinese girl was the second child of a healthy non-consanguineous Chinese couple. She had been born full-term by vaginal delivery with birth weight was 2.83 kg (below the 10th percentile); while her height was 48 cm. Her medical history revealed mild aortic valvular stenosis, mild septal hypertrophy and recurrent ear infections. She had undergone dental treatment under general anesthesia when she was six years and nine months old. Examination of the propositis' parents and her elder sister revealed that they were unaffected by the syndrome. Extra-orally, she presented with the characteristic features of a convex profile with a webbed neck, hypertelorism, low-set ears, characteristic facial expression and low posterior hairline. Intra-orally, she had a permanent dentition with poor oral hygiene and localized gingival inflammation in the anterior region of both jaws. She brushed her teeth twice daily and used dental floss daily. The clinical examination revealed a U-shaped maxillary arch, with a class III molar relationship, mild crowding in the maxillary arch, high arch palate, a maxillary right canine, and proclined mandibular incisors. The radiographic examination revealed the maxillary right canine to be in an ectopic position; there was taurodontism of the maxillary first permanent molars and agenesis of the maxillary third molars (Figure 2). Her weight and height were 26.6 kg (below the 3rd percentile) and 121 cm (below the 3rd percentile).

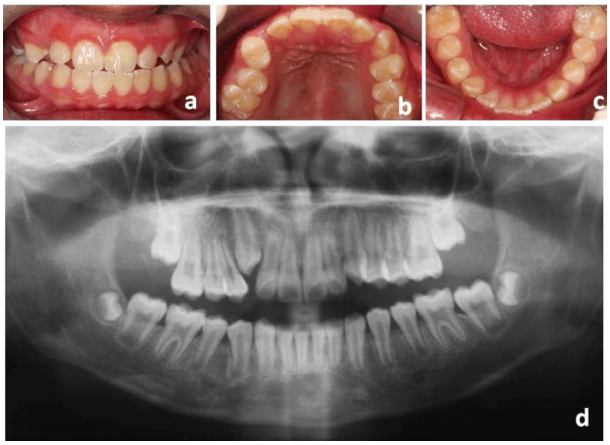

Figure 2 – *Case No. 2: (a) frontal view of the maxillary and mandibular arches, (b) occulsal view of maxillary arch, (c) mandibular arch, and (d) panoramic radiograph indicating impaction of tooth 13, and taurodontism of the maxillary first permanent molars.*

Case No. 3

A 11 years and 10 months old Chinese girl, who was the second child of a healthy non-consanguineous Chinese

couple. The girl had been born full-term by vaginal delivery and her birth weight of 3.24 kg and height of 51 cm. The medical history indicated that she had an atrial septal defect, pulmonary stenosis and that she was under regular review at the cardiology department in a private hospital. Her dental history revealed that previously she had received multiple tooth restorations and extractions. Extra-orally, she presented with a convex profile, low-set ears, a fixed facial expression and a low posterior hairline. She was in the mixed dentition with poor oral hygiene and gingival inflammation. Reportedly, she brushed her teeth twice daily. Her maxillary arch was parabolic; while the mandibular arch was U-shaped. Clinical examination revealed a class III malocclusion, with crowding in both the maxillary and mandibular arches, and generalized macrodontia. Gingival recession was observed in relation to tooth 41, due to traumatic occlusal relationship with tooth 11. Tooth 21 was partially erupted, and enamel hypoplasia was observed on the maxillary and mandibular incisors. Space discrepancies were evident in both the maxillary and mandibular arches. Radiographic examination revealed a dilaceration of tooth 21, taurodontism of the maxillary first permanent molars and agenesis of the third molars (Figure 3). Her body weight and height were found to be 26.5 kg (between 3rd and 10th percentile) and 123 cm (below the 3rd percentile) respectively. Her parents and elder sister were unaffected by the syndrome.

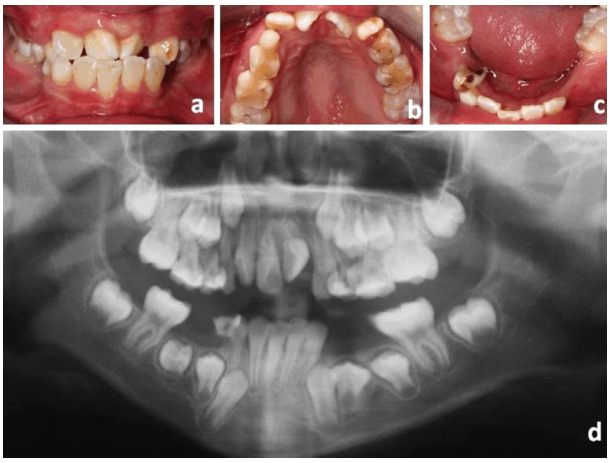

Figure 3 – ***Case No. 3 showing (a) frontal view of maxillary and mandibular arches, (b) occlusal view of maxillary arch, (c) occlusal view of mandibular arch, and (d) panoramic radiograph showing the dilaceration of tooth 21, congenital absence of all third molars and taurodontism of the maxillary first permanent molars.***

Case No. 4

A 15 years and 10 months old Chinese girl, who was the first child of a healthy non-consanguineous Chinese couple, had been born pre-term. Her birth weight was 2.1 kg (below the 3rd percentile), and height was 45 cm (below the 3rd percentile). Her past dental history revealed that she had received treatment under general anesthesia at 8-year-old. Two years later, a pyogenic granuloma in the 83 region was surgically removed under general anesthesia. Teeth 82 and 83 presented as a double tooth according to a previous radiograph (Figure 4).

Extra-orally, the patient exhibited a triangular face with a convex profile, flat base of the nose, low-setting ears, a webbed neck, fixed facial expression and low posterior hairline. She was in the permanent dentition and her oral hygiene was poor even though she brushed her teeth twice daily. The intra-oral examination revealed a class III malocclusion with crowding in the maxilla and mandible, generalized macrodontia, high arched palate, hypoplasia of the maxillary central incisors and the right mandibular second premolar. Tooth 15 is erupting palatally and tooth 63 is retained. The maxillary arch was parabolic; while the mandibular arch was U-shaped and teeth 23, 25 and 44 were impacted. There was also taurodontism of the first permanent molars, and agenesis of the maxillary third molars and one mandibular incisor (Figure 5). Currently, her body weight (23.5 kg) and height (123 cm) were below the 3rd percentile respectively.

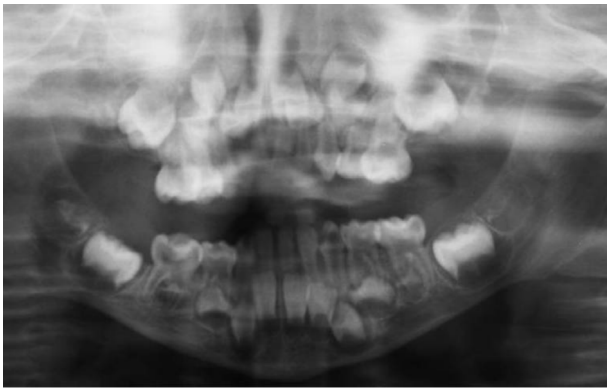

Figure 4 – ***Panoramic radiograph of Case No. 4 at the age of four years and six months showing the double tooth on the right side of the mandible and the congenitally missing permanent mandibular left central incisor.***

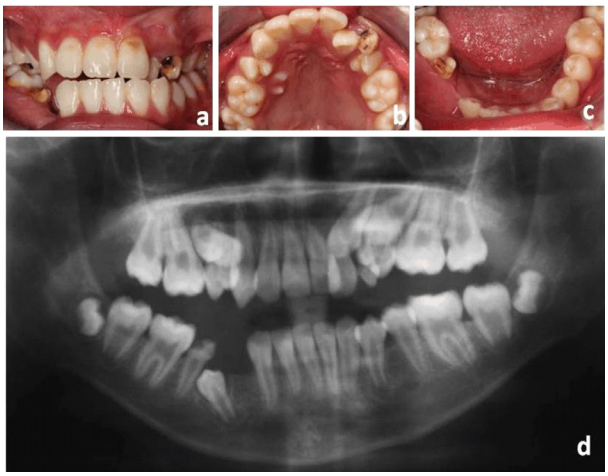

Figure 5 – ***Case No. 4: (a) frontal view of the maxillary and mandibular arches (b) occlusal view of maxillary arch, (c) occlusal view of mandibular arch, and (d) panoramic radiograph exhibiting impacted teeth 23, 25 and 44, taurodontic maxillary first permanent molars, and congenitally missing teeth 18, 28 and 42.***

Discussion

The diagnosis of NS can be made clinically, based on the diagnostic criteria given by van der Burgt *et al.* [40]. All four of the patients in the present report had the phenotypic characteristics of NS. Noonan syndrome

is a common autosomal dominant disorder, which involves multiple systems and typically is evident at birth. The clinical and oral manifestations of all of the patients are summarized in Table 2. The phenotypic features of NS vary significantly, especially if the diagnosis was not made at birth. Hence, it is important to appreciate the extent of phenotypic variations in affected individuals.

Table 2 – ***Summary of the general and oral manifestations of Noonan syndrome in four southern Chinese children***

Features	Case No. 1	Case No. 2	Case No. 3	Case No. 4
Age [years]	9.8	12.8	11.1	15.1
Behavioural problems	Y	Y	Y	Y
Cardiac problems	Y	Y	Y	Y
Chest deformity	Y	Y	Y	Y
Eye problems	Y	Y	Y	Y
Ear problems	N	N	N	N
Feeding difficulties	Y	Y	Y	Y
Gastrointestinal problems	N	N	N	Y
Gender	M	F	F	F
Growth problems	Y	Y	Y	Y
Height (percentile)	128 cm (<3rd)	120 cm (<3rd)	123 cm (<3rd)	123 cm (<3rd)
Hemotological problems	N	Y	N	Y
Lower posterior hair line	Y	Y	Y	Y
Oral manifestations	Enamel hypoplasia High arch palate Impacted teeth Macrodontia Malocclusion Micrognathia Taurodontism	High arch palate Hypodontia Impacted tooth Macrognathia Malocclusion Taurodontism	Dilaceration Enamel hypoplasia High arch palate Hypodontia Impacted teeth Malocclusion Microdontia Micrognathia Taurodontism	Double tooth Enamel hypoplasia Hypodontia Impacted teeth Malocclusion Microdontia Micrognathia Pyogenic granuloma Taurodontism
Orthopedic problems	N	Y	Y	Y
Renal problems	N	N	N	Y
Short stature	Y	Y	Y	Y
Webbed neck	Y	Y	Y	Y

Y: Yes; N: No; M: Male; F: Female.

Scully *et al.* [41] reported that the oral manifestations of NS may occur together or separately along with the general manifestations. The present review demonstrated that the distribution of dental findings was not consistent with that reported in the literature, and that not all of the oral features of NS are evident in all cases. The most commonly reported oral findings in NS seem to include high arch palate, micrognathism, malocclusions, giant cell lesions, and anomalous lateral incisors. There are several reports of hypodontia [35], retroclined mandibular incisors [34, 36] periodontal problems [22, 35], supernumerary teeth [34, 39], neurofibromatosis [29], and multiple odontogenic keratocysts [18]. van der Burgt *et al.* [40] developed a scoring system for the diagnosis of NS, which is displayed in Table 3.

Table 3 – ***Scoring system for the diagnosis of Noonan syndrome [40]***

Feature	Major	Minor
Facial	Typical face dysmorphology	Suggestive face dysmorphology
Cardiac	Pulmonary valve stenosis	Other defect
Height	<3rd percentile	<10th percentile
Chest wall	Pectus carinatum/ excavatum	Broad thorax
Family history	First degree relative with definite NS	First degree relative with suggestive NS
Other	Mental retardation, cryptorchidism and lymphatic dysplasia	Mental retardation or cryptorchidism or lymphatic dysplasia

According to this system, there should be one major and two minor signs or one minor and two major signs in order to make a definitive diagnosis of NS. We would like propose score 4 for major sign and score 2 for minor sign respectively, with this score if any individual with NS should have at least two major and one minor (score 10) or one major and three minor signs (score 10), or five minor signs (score 10). Interestingly, all of the patients in the present report predominantly exhibited three major and three minor signs [40] and the score for our four patients according to the proposed scoring system was 18.

Consistent with the literature, our four cases exhibited malocclusion, high arch palate, micrognathia, hypodontia and taurodontism. In addition, macrodontia, enamel hypoplasia and double tooth were also observed. The oral manifestations may result in feeding difficulties, and facial growth problems, which may require management by a multidisciplinary team. Therefore, it is essential that clinicians understand the nature and extent of the variations in the clinical presentations of individuals with NS, so as to be proficient in the diagnosis. Families with a member affected by NS should undergo genetic counseling to educate them on the consequences and risk of transmission to their offsprings [42]. Ascertaining the diagnosis of NS can be difficult, particularly in adulthood, because of the diverse presentations of the phenotype, which may even become less pronounced with increasing age [14].

Oral health care for NS patients should commence in the first year of life, in order to prevent the problems from becoming irreversible. Therefore, preventive strategies are

recommended, with customized protocols which focused on a rehabilitative process so as to normalize the musculature of the lower third of the face, which is often compromised in NS [37]. It is important to monitor the oral health of the patients with NS, because they are prone to severe dental caries [27] and gingival problems [22, 36, 37]. Prevention of early childhood caries is important, to avoid subsequent problems during the eruption of the permanent teeth [18, 22–26, 36–39]. Moreover, early identification and management of dental anomalies are important.

Conclusions

The oral manifestations of NS have not been extensively described in the literature. Based on the four presented cases, we suggest that high arch palate, micrognathia, macrodontia, enamel hypoplasia, hypodontia and taurodontism are features that are consentingly associated with NS. Furthermore, we propose that these oral manifestations should be incorporated into the scoring criteria for the diagnosis of NS.

References

[1] Nora JJ, Nora AH, Sinha AK, Spangler RD, Lubs HA, *The Ullrich–Noonan syndrome (Turner phenotype)*, Am J Dis Child, 1974, 127(1):48–55.

[2] Romano AA, Allanson JE, Dahlgren J, Gelb BD, Hall B, Pierpont ME, Roberts AE, Robinson W, Takemoto CM, Noonan JA, *Noonan syndrome: clinical features, diagnosis, and management guidelines*, Pediatrics, 2010, 126(4):746–759.

[3] Kobylinski O, *Über eine flughautahnliche Ausbreitung am Halse*, Arch Anthropol, 1883, 14:343–348.

[4] Noonan JA, Ehmke DA, *Associated noncardiac malformations in children with congenital heart disease*, J Pediatr, 1963, 63:468–470.

[5] Noonan JA, *Hypertelorism with Turner phenotype. A new syndrome with associated congenital heart disease*, Am J Dis Child, 1968, 116(4):373–380.

[6] Ford CE, Jones KW, Polani PE, de Almeida JC, Briggs JH, *A sex-chromosome anomaly in a case of gonadal dysgenesis (Turner's syndrome)*, Lancet, 1959, 1(7075):711–713.

[7] Sharland M, Burch M, McKenna WM, Patton MA, *A clinical study of Noonan syndrome*, Arch Dis Child, 1992, 67(2):178–183.

[8] Tartaglia M, Gelb BD, *Noonan syndrome and related disorders: genetics and pathogenesis*, Annu Rev Genomics Hum Genet, 2005, 6:45–68.

[9] Jongmans M, Sistermans EA, Rikken A, Nillesen WM, Tamminga R, Patton M, Maier EM, Tartaglia M, Noordam K, van der Burgt I, *Genotypic and phenotypic characterization of Noonan syndrome: new data and review of the literature*, Am J Med Genet A, 2005, 134A(2):165–170.

[10] Tartaglia M, Kalidas K, Shaw A, Song X, Musat DL, van der Burgt I, Brunner HG, Bertola DR, Crosby A, Ion A, Kucherlapati RS, Jeffery S, Patton MA, Gelb BD, *PTPN11 mutations in Noonan syndrome: molecular spectrum, genotype-phenotype correlation, and phenotypic heterogeneity*, Am J Hum Genet, 2002, 70(6):1555–1563.

[11] Tartaglia M, Martinelli S, Stella L, Bocchinfuso G, Flex E, Cordeddu V, Zampino G, Burgt Iv, Palleschi A, Petrucci TC, Sorcini M, Schoch C, Foa R, Emanuel PD, Gelb BD, *Diversity and functional consequences of germline and somatic PTPN11 mutations in human disease*, Am J Hum Genet, 2006, 78(2):279–290.

[12] Noordam C, Van der Burgt I, Sengers RC, Delemarre-van de Waal HA, Otten BJ, *Growth hormone treatment in children with Noonan's syndrome: four year results of a partly controlled trial*, Acta Paediatr, 2001, 90(8):889–894.

[13] Limal JM, Parfait B, Cabrol S, Bonnet D, Leheup B, Lyonnet S, Vidaud M, Le Bouc Y, *Noonan syndrome: relationships between genotype, growth, and growth factors*, J Clin Endocrinol Metab, 2006, 91(1):300–306.

[14] Allanson JE, Hall JG, Hughes HE, Preus M, Witt RD, *Noonan syndrome: the changing phenotype*, Am J Med Genet, 1985, 21(3):507–514.

[15] Allanson JE, *Noonan syndrome*, J Med Genet, 1987, 24(1): 9–13.

[16] Shaw AC, Kalidas K, Crosby AH, Jeffery S, Patton MA, *The natural history of Noonan syndrome: a long-term follow-up study*, Arch Dis Child, 2007, 92(2):128–132.

[17] Baird PA, De Jong BP, *Noonan's syndrome (XX and XY Turner phenotype) in three generations of a family*, J Pediatr, 1972, 80(1):110–114.

[18] Nelson JF, Tsaknis PJ, Konzelman JL, *Noonan's syndrome: report of a case with oral findings*, J Oral Med, 1978, 33(3): 94–96.

[19] Chuong R, Kaban LB, Kozakewich H, Perez-Atayde A, *Central giant cell lesions of the jaws: a clinicopathologic study*, J Oral Maxillofac Surg, 1986, 44(9):708–713.

[20] Dunlap C, Neville B, Vickers RA, O'Neil D, Barker B, *The Noonan syndrome/cherubism association*, Oral Surg Oral Med Oral Pathol, 1989, 67(6):698–705.

[21] Cohen MM Jr, Gorlin RJ, *Noonan-like/multiple giant cell lesion syndrome*, Am J Med Genet, 1991, 40(2):159–166.

[22] Torres-Carmona MA, Arenas-Sordo ML, Saavedra-Ontiveros D, Sánchez-Guerrero MC, *Enfermedad periodontal en el síndrome de Noonan (Periodontal disease in the Noonan syndrome)*, Bol Méd Hosp Infant Mex, 1991, 48(4):271–274.

[23] Sugar AW, Ezsias A, Bloom AL, Morcos WE, *Orthognathic surgery in a patient with Noonan's syndrome*, J Oral Maxillofac Surg, 1994, 52(4):421–425.

[24] Lucker GP, Steijlen PM, *Widespread leucokeratosis in Noonan's syndrome*, Clin Exp Dermatol, 1994, 19(5): 414–417.

[25] Addante RR, Breen GH, *Cherubism in a patient with Noonan's syndrome*, J Oral Maxillofac Surg, 1996, 54(2):210–213.

[26] Nirmal T, Muthu MS, Arranganal P, *Noonan syndrome: a case report*, J Indian Soc Pedod Prev Dent, 2001, 19(2):77–79.

[27] Barberia Leache E, Saavedra Ontiveros D, Maroto Edo M, *Etiopathogenic analysis of the caries on three patients with Noonan Syndrome*, Med Oral, 2003, 8(2):136–142.

[28] Okada M, Sasaki N, Kaihara Y, Okada R, Amano H, Miura K, Kozai K, *Oral findings in Noonan syndrome: report of a case*, J Oral Sci, 2003, 45(2):117–121.

[29] Yazdizadeh M, Tapia JL, Baharvand M, Radfar L, *A case of neurofibromatosis-Noonan syndrome with a central giant cell granuloma*, Oral Surg Oral Med Oral Pathol Oral Radiol Endod, 2004, 98(3):316–320.

[30] Edwards PC, Fox J, Fantasia JE, Goldberg J, Kelsch RD, *Bilateral central giant cell granulomas of the mandible in an 8-year-old girl with Noonan syndrome (Noonan-like/multiple giant cell lesion syndrome)*, Oral Surg Oral Med Oral Pathol Oral Radiol Endod, 2005, 99(3):334–340.

[31] Asokan S, Muthu MS, Rathna Prabhu V, *Noonan syndrome: a case report*, J Indian Soc Pedod Prev Dent, 2007, 25(3): 144–147.

[32] Cancino CMH, Gaião L, Sant'Ana Filho M, Oliveira FAM, *Giant cell lesions with a Noonan-like phenotype: a case report*, J Contemp Dent Pract, 2007, 8(4):67–73.

[33] Sharma PR, MacFadyen UM, Fung DE, *Dental management of a child patient with Noonan's syndrome*, Dent Update, 2007, 34(2):117–118, 120.

[34] Ortega Ade O, Guaré Rde O, Kawaji NS, Ciamponi AL, *Orofacial aspects in Noonan syndrome: 2 case report*, J Dent Child (Chic), 2008, 75(1):85–90.

[35] Sahebjamee M, Ameri NG, Farhud DD, *First report of new oral findings in a case with Noonan syndrome*, Iranian J Publ Health, 2008, 37(4):131–137.

[36] Emral ME, Akcam MO, *Noonan syndrome: a case report*, J Oral Sci, 2009, 51(2):301–306.

[37] Ierardo G, Luzzi V, Panetta F, Sfasciotti GL, Polimeni A, *Noonan syndrome: a case report*, Eur J Paediatr Dent, 2010, 11(2):97–100.

[38] Bufalino A, Carrera M, Carlos R, Coletta RD, *Giant cell lesions in Noonan syndrome: case report and review of the literature*, Head Neck Pathol, 2010, 4(2):174–177.

[39] Toureno L, Park JH, *Atypical orofacial conditions in Noonan syndrome: a case report*, J Clin Pediatr Dent, 2011, 36(2): 197–202.
[40] van der Burgt I, Berends E, Lommen E, van Beersum S, Hamel B, Mariman E, *Clinical and molecular studies in a large Dutch family with Noonan syndrome*, Am J Med Genet, 1994, 53(2):187–191.
[41] Scully C, Langdon J, Evans J, *Marathon of eponyms: 14 Noonan syndrome*, Oral Dis, 2010, 16(8):839–840.
[42] Noonan JA, Raaijmakers R, Hall BD, *Adult height in Noonan syndrome*, Am J Med Genet A, 2003, 123A(1):68–71.

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