Atypical Orofacial Conditions in Noonan Syndrome: A Case Report

Leo Toureno * / Jae Hyun Park **

Noonan syndrome (NS) is a relatively common condition characterized by chest deformation, congenital heart disease, short stature and distinctive facial features. Due to its genetic heterogeneity NS patients exhibit a range of clinical signs. Severe gingivitis and supernumerary teeth are rarely seen in connection with NS. In addition, there has not been a report on NS patients with atypical bilateral enlargement of the mental foramens and inferior-alveolar canals. This case report describes a NS patient who has undergone growth hormone (GH) therapy and is presenting with classical and rare NS phenotypes.
Keywords: *Noonan syndrome (NS), growth hormone (GH), supernumerary teeth*
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INTRODUCTION

Noonan syndrome (NS) was first described about 47 years ago by Jacqueline Noonan, a pediatric cardiologist, who identified nine patients who were short of stature, had significant chest deformations, pulmonary stenosis and whose faces were remarkably similar.[1] Not until the first decade of the twenty-first century has there been a genetic explanation for the condition.[1,2] PTPN11 (protein tyrosine phosphatase non–receptor type 11) missense mutation was identified in 2001 by Tartaglia *et al*[3] as the first molecular basis for NS. SHP-2 (Src homology 2-containing tyrosine phosphatase), a product of the PTPN11 gene, is a protein tyrosine phosphatase with a positive regulatory role in Ras/MAPK (rat sarcoma/mitogen-activated protein kinase) signaling—it participates in downstream signaling of several ligand-receptor complexes with possible relevance to the pleiomorphic abnormalities observed in NS [for example, fibroblast growth factor for bone development, growth hormone (GH) and insulin-like growth factor (IGF) for somatic growth].[2]

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NS is characterized by distinct features including hypertelorism, down-slanting palpebral fissures, a high arched palate, low set posteriorly rotated ears, malar hypoplasia, ptosis and a short or webbed neck.[1] Scientists have discovered that mutations in the PTPN11 gene are the primary cause of NS, but there appears to be a variation of phenotypes since the main genetic mutation is present in only about 40% of NS patients.[1] Genes other than Ras/MAPK were then considered as candidate genes that might be mutated in NS patients: (1) KRAS (V-Ki-ras2 Kirsten rat sarcoma viral oncogene homolog);[4,5] (2) NRAS (neuroblastoma RAS viral (v-ras) oncogene homolog);[6] (3) SOS1 (son of sevenless homolog 1);[7] (4) RAF1 (v-raf-1 murine leukemia viral oncogene homolog 1);[8,9] (5) BRAF (v-raf murine sarcoma viral oncogene homolog B1);[10] and (6) SHOC2 [soc-2 (suppressor of clear) homolog (C. elegans)][11] that may explain some of the other NS cases not attributed by PTPN11. Even so, almost 40% of all NS patients cannot be attributed to any of these genes, so additional gene candidates will need to be identified in the future.

Case Report

A 14 year 8 month old male presented to the orthodontic clinic with the primary complaint that "his canines were sticking out." Upon initial observation, he was found to be of short stature, had a relatively large nose, down-slanting palpebral fissures, low set posteriorly rotated ears, full lips, a short neck, and his face shape was like an inverted triangle, wide at the forehead and tapered to a pointed chin. He had a tendency for lip incompetence and stated that he had a habit of breathing through his mouth. He appeared to be cognitively normal and was able to communicate and follow instructions (Figure 1).

Intraoral examination revealed localized severe gingivitis and associated plaque in the canine and first premolar regions and a high arched palate. There was also gingivitis

Figure 1. Facial photo.

around some of the anterior teeth in contrast to most of the posterior gingival tissue which appeared relatively healthy. The patient also had severe crowding of the maxillary and mandibular arches with blocked out canines. In addition, the maxillary canines and the mandibular left canine were

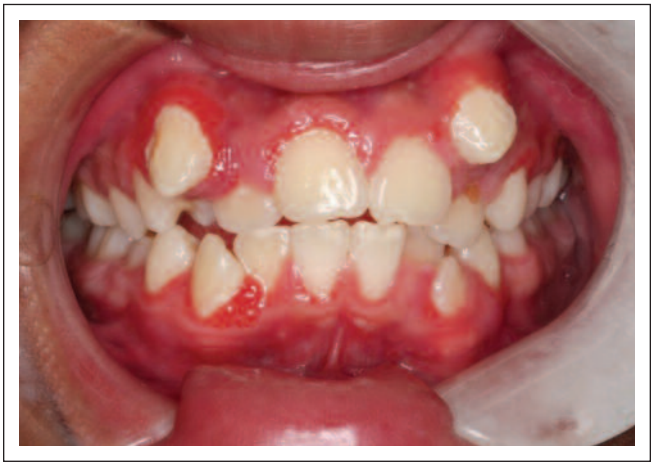

Figure 2. Frontal intraoral picture in centric occlusion; note the severe gingivitis and dental crowding.

ectopically erupted. The patient's teeth appeared to be larger than normal but Bolton's analysis indicated no discrepancy in tooth size between the maxillary and mandibular arches. He presented with Angle's Class I malocclusion with an edge to edge open bite tendency. His mandibular dental midline was shifted to the right by approximately 2 mm (Figure 2).

Panoramic radiograph revealed symmetrical supernumerary tooth buds distoapically to the first premolars in all four quadrants, large bilateral inferior-alveolar canals and large mental foramens (Figure 3). The patient also reported having

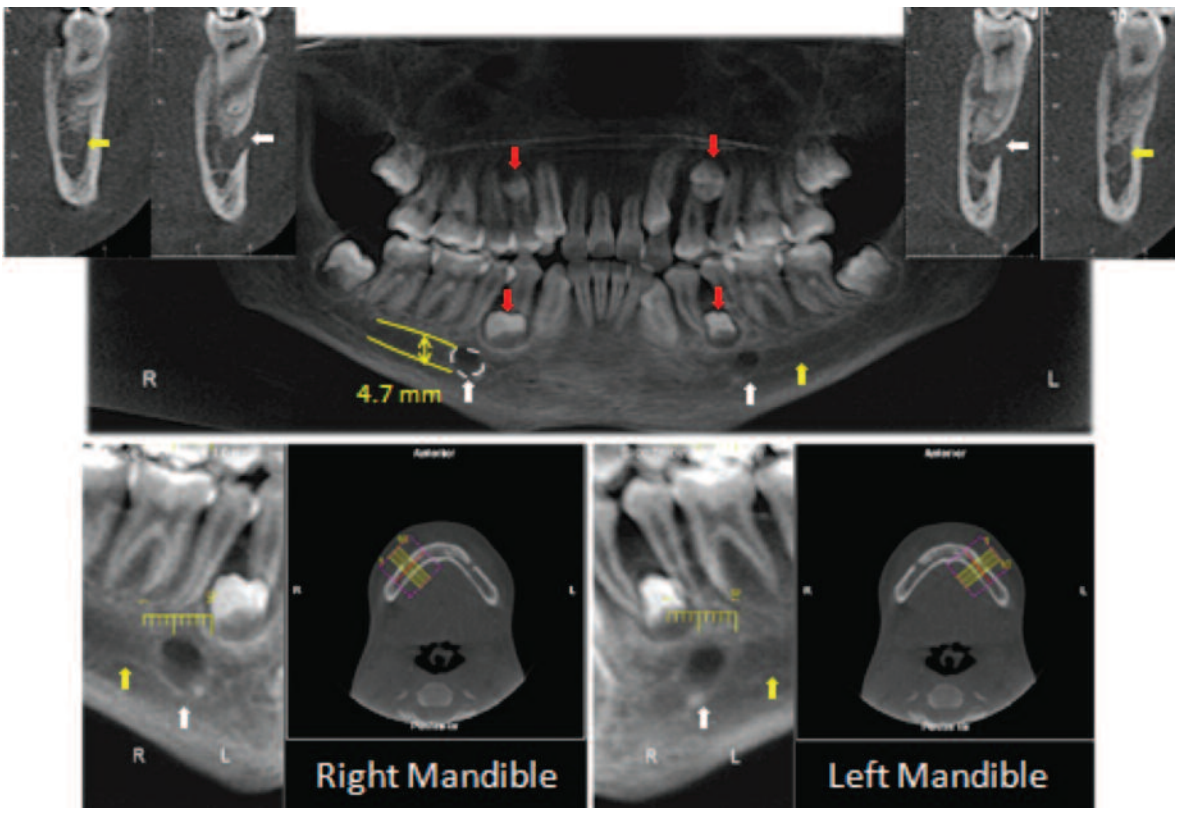

Figure 3. The supernumerary teeth (red arrows) #55, 62, 71, 78 (corresponding to #5, 12, 21 and 28 respectively)[27] and the large oval bilateral mental foramens (D: 4 x 5 mm) and inferior alveolar canals (D: 4.7 mm average size) from the CBCT images. White arrows (mental foramens); yellow arrows (inferior alveolar canals).

had 5 additional supernumerary teeth removed by an oral surgeon three years earlier.

Lateral Cephalometric analysis showed Class II skeletal pattern (ANB: 9.8˚) and an increased lower anterior facial height (LFH: 59.4%). Because of the clockwise rotation of the jaws relative to SN, Wits revealed -1.5 mm along with a hyperdivergent growth pattern (SN-MP: 44.9˚). The maxillary incisors were slightly retroclined (U1 to SN: 99.7˚) while the mandibular incisors were proclined (IMPA: 104.6˚). The patient's cervical vertebrae appeared to be normal with no fusion (Figure 4 and Table I).

The patient was diagnosed with Noonan syndrome when he was 12 years old and was referred to a pediatric endocrinologist for an evaluation of possible growth hormone (GH) therapy due to his height which was below the 1st percentile. Furthermore, using the Radiographic Atlas of Skeletal Development of the Hand and Wrist by Greulich and Pyle,[12] the patient exhibited greater than 2 standard deviations between his chronological age and skeletal bone age implying a developmental delay (G. Hernandez, M.D., written communication, May 26, 2009). He was started on GH (Nutropin AQ, 2.2mg) daily injections when he was 12 years and 11 months old. He responded by showing some growth but he barely crossed into the 3rd percentile for height after 1 year and 9 months of GH treatment (Figure 5).[13] The pediatric endocrinologist and the patient's parents are currently contemplating using Femara, a non-steroidal aromatase inhibitor, to keep the growth plates in the long bones open until the targeted height and weight are achieved. Fortunately, his pediatric endocrinologist reported the patient had no back problems or issues with scoliosis (E. Holland, M.D., written communication, November 20, 2008). His medical history is negative for any other medical condition or past surgeries.

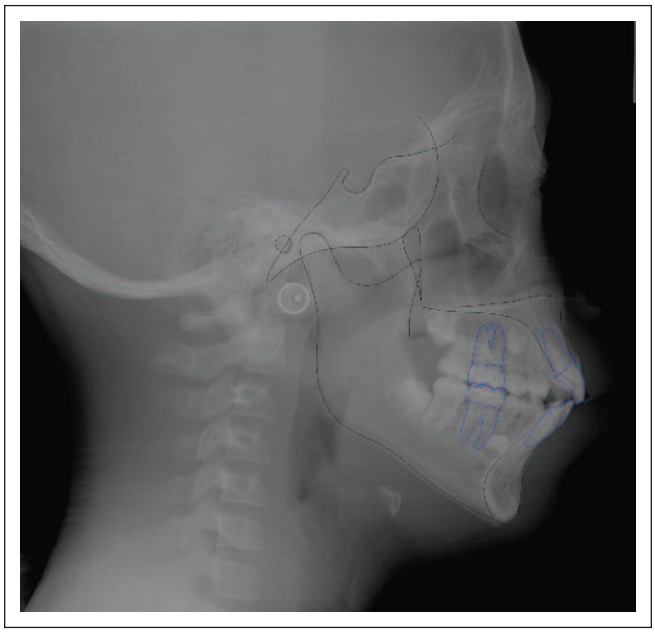

Figure 4. Traced lateral cephalometric radiograph.

Table I. Summary of cephalometric measurements.

Measurement	Norm	SD	Case
SNA (°)	82	3.5	81.3
SNB (°)	80	3.1	71.5
ANB (°)	2	1.5	9.8
Wits (mm)	1.1	2	-1.9
SN-MP	32	5.2	44.9
FH-MP	25	4.5	30.5
LFH(ANS-Me/N-Me) (%)	55	0.1	59.4
U1 to SN (°)	104	5.5	99.7
U1 to NA (°)	22	5	18.4
IMPA (°)	90	7	104.6
L1 to NB (°)	25	6	43.7
Upper lip to E-Plane (mm)	-4	2	2
Lower lip to E-Plane (mm)	-2	2	6.2

SD, standard deviation.

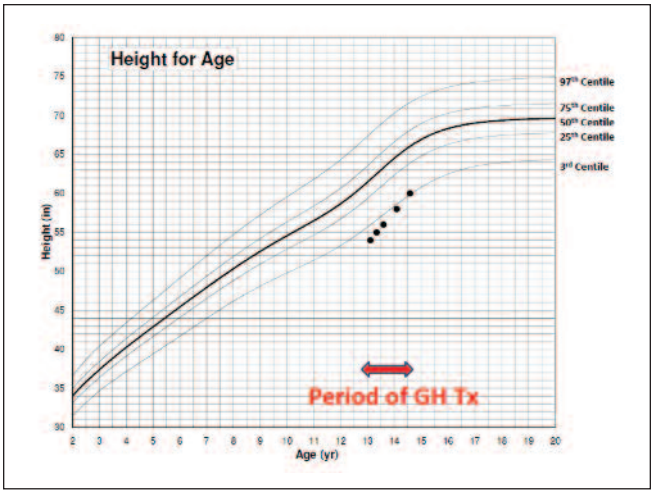

Figure 5. Stature-by-age percentiles for boys (inches vs. age).[13] Patient data is represented by black dots; he started GH treatment before the first dot at age 12 years and 10 months. The patient was below the 3rd percentile until the last visit with the endocrinologist (last dot) when he barely made the 3rd percentile.

DISCUSSION

Our case report reinforces the fact that NS is variable in phenotype due to its genetic heterogeneity. The patient presents with many common NS features such as shortness of stature, down-slanting palpebral fissures, low set posteriorly rotated ears, full lips, a short neck, and his face shape is like an inverted triangle, wide at the forehead and tapered to a pointed chin (Figure 1). Furthermore he exhibits a high arched palate,[14-17] an anterior open bite tendency (edge to edge bite),[17-19] prognathic mandible[17-20] and dental malocclusion common in NS patients.[14-19] However, he also exhibits uncommon (or less reported) features such as severe localized gingivitis, supernumerary teeth, large inferior-alveolar canals and mental foramens, and he is negative for cardiac issues and bleeding disorders which are common for NS patients (Table II).[2] In contrast to our patient with localized severe gingivitis around the canines and first premolars, most dental case reports of NS patients were negative for severe gingivitis[17,18,20,21] Only two articles reported periodontal issues: Ortega *et al*[22] noted generalized gingival inflammation in two adolescent cases (although the intraoral pictures did not show much gingival inflammation); Sugar *et al*[19] indicated periodontal problems that precluded their 22

year old patient from undergoing orthodontic treatment. Although gingivitis is not the same as periodontal disease but is merely a precursor, it is interesting to note that periodontal disease seems to be absent in acromegalic patients (excessive GH).[23] One can imply that the opposite may be true for GH deficient patients. Although not based on a NS patient, Buduneli *et al* [24] noted severe gingival inflammation with layers of calculus and multiple dental caries in the GH deficient subject. Notwithstanding our patient's supposed lack of GH, his habit of breathing through his mouth and tendency for lip incompetence may have contributed to his severe gingivitis especially considering that most of the inflammation occurred in the anterior region of his mouth. In support of this hypothesis, two studies[25,26] found that lip incompetence and mouth breathing habits are significantly associated with gingivitis.

It is interesting to note that the patient had supernumerary teeth in the first premolar regions of all four quadrants (Figure 3). Several case reports did not indicate any supernumerary teeth in NS;[17,18,20] while Emral *et al*[21] reported congenitally missing teeth. Only Ortega *et al*[22] reported the presence of 2 supernumerary lateral incisors in one of his cases. In addition, the patient stated that he had 5 permanent supernumerary teeth removed by an oral surgeon 3 years earlier (J Gillis, DMD, written communication, November 2010). The oral surgeon noted the supernumerary teeth as follows: #56, #58, #59, #72 and #77. According to the Universal Tooth Numbering System these are in proximity to the following teeth respectively: #6, #8, #9, #22 and #27.[27] In total, the patient had nine supernumerary teeth which is very rare according to the review on supernumerary teeth.[28]

None of the NS dental case reports and none of the medical NS articles identified bilateral large oval mental foramens and inferior-alveolar canals (average sizes of 4 x 5 mm and up to 5.6 mm in diameter respectively, measured from CBCT scan), but we noted such an anomaly in our NS patient (Figure 3). Gershenson *et al*[29] studied 525 dry mandibles and 50 cadaver dissections and found that the mental foramen was round in 34.48% of the cases with an average diameter of 1.68 mm and oval 65.52% of the time with an average long diameter of 2.37 mm. Since Meckel's cartilage is involved with the formation of the mandible and the inferior alveolar canal,[30] we hypothesize that a dysfunctional intra-membranous ossification process may have caused the atypically sized canal. Another reason explaining the large inferior alveolar canals and foramens may be the involvement of the Ras/MAPK pathway which is common to both NS and neurofibromatosis (NF).[31] Two studies[32,33] reported that a widening of the inferior alveolar canal is a sign of NF. Interestingly, several case reports have identified the coexistence of NS and NF patients.[31,34] At this time, we can only speculate regarding our patient's status as the NS-NF genotype. An abnormally large inferior-alveolar canal and mental foramen must cue the dentist or oral surgeon to be more careful when extracting impacted supernumerary premolar tooth buds. Further, if in the future the patient needs a dental implant in the posterior segment of the arch, CBCT images may be prudent to reduce the potential of injury to vital structures.

Although our patient lacked bleeding disorders and congenital heart disease (CHD), these issues are common in NS.[1,2,35] Dentists may need to order PT (prothrombin time) to assess the safety of invasive dental procedures such as extractions. With regards to CHD, dentists may also need to

Table II. Previously reported cases of dental and oral findings of NS patients.

Author/year	Age	Sex	Open bite	High palate	Malocclusion	Mandible	Ectopic / Transposition	Supernumerary tooth (# of teeth)	Gingivitis/ Periodontitis	Caries	GH treatment	Other
Horowitz et al. 1974[44]												
6 cases			no	yes	yes	NR	NR	NR	NR	NR	NR	
Nelson et al. 1978[45]	6	M	NR	yes	NR	NR	NR	NR	NR	no	NR	oral xanthoma
Dunlap et al. 1989												
4 cases[46]			NR	NR	NR	NR	NR	NR	NR	NR	NR	cherubism
Levine et al. 1991[47]	8	M	NR	NR	yes	retrognathic	NR	NR	NR	no	NR	cherubism
Sugar et al. 1994[19]	22	M	yes	NR	yes	prognathic	NR	NR	yes	NR	NR	anterior crossbite
Addante et al. 1996[48]	4	M	NR	NR	NR	NR	NR	NR	NR	NR	NR	cherubism
Nirmal et al. 2001[49]	4	M	NR	yes	NR	NR	NR	NR	NR	yes	NR	
Okada et al. 2003[17]	8	M	yes	yes	yes	retrognathic	NR	no	no	no	NR	posterior crossbite
Leache et al. 2003[20]												
Case 1	4	F	NR	NR	no	NR	NR	NR	NR	yes	NR	
Case 2	4	M	yes	NR	yes	NR	NR	NR	NR	yes	NR	
Case 3	9	M	NR	NR	yes	NR	NR	NR	NR	yes	NR	
Asokan et al. 2007[18]	13	F	yes	yes	yes	prognathic	yes	no	no	yes	NR	
Sharma et al. 2007[50]	9	F	NR	NR	yes	NR	NR	NR	yes	yes	NR	
Ortega et al. 2008[22]												
Case 1	14	M	no	NR	yes	retrognathic	NR	no	yes	yes	NR	posterior crossbite
Case 2	13	M	no	NR	yes	prognathic	NR	yes (2)	yes	yes	NR	
Emral et al. 2009[21]	13	M	no	yes	yes	orthognathic	yes	no	NR	no	NR	congenitally missing teeth, deep bite
Ierardo et al. 2010[51]	8	F	no	NR	no	orthognathic	yes	no	no	NR	NR	congenitally missing teeth, deep bite
Bufalino et al. 2010[52]	8	M	NR	NR	NR	NR	NR	NR	NR	NR	NR	cherubism

NR, not reported.

assess the need to prescribe antibiotic prophylaxis for NS patients who have unrepaired CHD or prosthetic heart valves.[36]

The patient had been on GH therapy for 1 year and 9 months but the target height for the patient had not been reached. The latest bone age assessment indicated that he was still more than 2 standard deviations below his chronological age. His endocrinologist suggested that he had time to grow and that his bone age was advanced enough that Femera should be implemented to keep the bone growth plates open, thus facilitating a continued increase in height.

Based on a review of literature regarding GH therapy for NS patients, the treatment remains controversial. On one hand, Ranke[37] questions the efficacy of GH therapy for NS patients and suggests more research needs to be conducted in the future while two studies[38,39] suggest that GH therapy is effective, especially if started early enough but they also found that the most obvious effect was seen in only the first 2 years of treatment. Otten *et al*[40] imply in their article that growth in NS patients who have not received GH treatment may just be delayed, that growth beyond the normal pubertal period may still occur. Hwang *et al*[41] suggest that orthodontic treatment be delayed until after GH treatment is completed due to the unpredictable growth pattern of the mandible. On the other hand, Hass *et al*[42] report no statistically significant effects of GH on mandibular growth with their study of Turner syndrome subjects. Kjellberg *et al*[43] report that GH deficient boys treated with GH had a favorable mandibular growth pattern when treatment was combined with orthodontics.

In light of our literature review on NS and GH therapy, we have decided to recommend going ahead with orthodontic treatment but have delayed it for a few months while we monitor the patient's growth through consultation with his endocrinologist. Furthermore, we plan to refer the patient to a periodontist for a periodontal evaluation and to his dentist for the restoration of several minor carious lesions. Our treatment plan for the patient involves the extraction of 4 supernumerary premolars and 4 permanent first premolars (which were indicated due to the severe crowding on the maxillary and mandibular arches) followed by the use of a fixed orthodontic appliance.

While the patient's orthodontic treatment is being postponed for a few months, we cannot rule out the fact that his growth may continue even into his twenties. In spite of this, we feel his psychological need for orthodontic treatment is greater than the potential downside, so we have informed the patient and his parents that post-orthodontic changes resulting from late growth may indicate additional treatment with or without orthognathic surgery. We also suggested that the patient have frequent dental follow up with proper oral hygiene care to prevent dental caries and periodontal issues.

CONCLUSION

Dentists are encouraged to care for special needs patients. Patients with NS present with a wide variation in phenotype including the characteristic short stature, down-slanting palpebral fissures, low set posteriorly rotated ears, full lips, a short or webbed neck and the less common supernumerary teeth, severe gingivitis, large inferior-alveolar canals and mental foramens. In addition to proper oral hygiene and caries reduction protocols, dental management of these patients includes assessing their bleeding time and the need for antibiotic prophylaxis. If orthodontic treatment is indicated, their growth potential with or without GH therapy needs to be considered.

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