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The Palatal and Oral Manifestations of Muenke Syndrome (FGFR3 related craniosynostosis)

Nneamaka B. Agochukwu, B.S.[1,2,a], **Benjamin D. Solomon, M.D.**[1], **Emily S. Doherty, M.D.**[3], and **Maximilian Muenke, M.D.**[1,*]

[1]Medical Genetics Branch, National Human Genome Research Institute, National Institutes of Health, Bethesda, MD, USA

[2]Clinical Research Training Program, National Institutes of Health, Bethesda, MD, USA

[3]Carilion Pediatric Clinic, Roanoake, VA

Abstract

Palatal anomalies including cleft palate and higharched palate have been reported in the most common craniosynostosis syndromes, including Pfeiffer syndrome (associated with mutations in *FGFR1, FGFR2*), Apert syndrome (*FGFR2*), Muenke syndrome (*FGFR3*) and Crouzon syndrome (*FGFR2*).

Although Muenke syndrome is the most common syndromic form of craniosynostosis, the frequency of oral and palatal anomalies including high arched palate, cleft lip with or without cleft palate has not been documented in a patient series of Muenke syndrome to date. Further, to our knowledge, cleft lip and palate has not been reported yet in a patient with Muenke syndrome (a previous patient with isolated cleft palate has been reported). This study sought to evaluate the frequency of palatal anomalies in patients with Muenke syndrome through both a retrospective investigation and literature review. A total of 21 patients who met criteria for this study were included in the retrospective review. 15 patients (71%) had a structural anomaly of the palate. Cleft lip and palate was present in one patient (5%). Other palatal findings included: high arched hard palate in 14 patients (67%). Individuals with Muenke syndrome have the lowest incidence of cleft palate among the most common craniosynostosis syndromes. However, high arched palate in Muenke syndrome is common and may warrant clinical attention, as these individuals are more susceptible to recurrent chronic otitis media with effusion, dental malocclusion and hearing loss.

Keywords

FGFR craniosynostosis palate; Palate Muenke Syndrome; Cleft Lip and Palate Craniosynostosis; FGFR3 craniosynostosis; Muenke syndrome

Introduction

A large proportion of midline anomalies are mostly closure defects, or defects of incomplete differentiation, and include midface, lip, palatal, jaw and laryngeal clefts, tracheoesophageal fistulas, congenital heart defects (VSD, ASD), midline diaphragm defects, hypospadias, imperforate anus, uterus didelphys and so forth.

[*]Corresponding author: Maximilian Muenke, NIH, MSC 3717, Building 35, Room 1B-203, Bethesda, MD USA 20892, Phone: 301-402-8167, Fax: 301-496-7184, mamuenke@mail.nih.gov.
[a]Present address: Vanderbilt University School of Medicine, 201 Light Hall, Nashville, TN 37232-0685, United States

A very common midline anomaly, which is the result of a defect of midline closure is cleft lip with or without cleft palate (CL/P), which has an incidence of approximately 1 in 700 births.[1] There is wide variability in the incidence of cleft lip and palate, depending on geographic origin, racial and ethnic background, environmental exposure, and socioeconomic status.[2–5] The highest reported birth prevalence rates are found in Asian and Native American populations, with reported prevalences as high as 1 in 500 births. This is followed by European-derived populations and African-derived populations with prevalence rates of 1 in 1,1000 and 1 in 2,500, respectively. These complexities in the epidemiology of CLP suggest varying contributions of individual susceptibility genes across different populations.[6–9] Further, the occurrence of CLP varies by both gender and sidedness: females are 2 times more likely than males to have cleft lip, whereas males are 2 times more likely to have cleft palate.[1] Additionally, among patients with unilateral cleft lip, patients are 2 times more likely to have left than right sided clefts.

Approximately 70% of all cases of CLP and 50% of cases of cleft palate only are nonsyndromic, occurring without additional associated anomalies.[9–11] It is of importance to note that “nonsyndromic” is merely a term to describe the absence of additional anomalies; it does not mean that these cases do not have a genetic basis, contribution or cause, or that genetic variants are less causally-related. The remaining syndromic cases (30% of cases of CLP and 50% of cases of cleft palate) consist of a wide range of malformation syndromes, including over 500 Mendelian syndromes as well as those arising secondary to chromosomal or teratogenic effects.

There are a number of growth and signaling factors that play a role in facial development, whose absent or aberrant signaling results in clefting. These involve genes encoding proteins such as the Transforming Growth Factor B family and their receptors (TGF-B, TGFBR), members of the Bone Morphogenetic Protein (BMP) family, Fibroblast Growth Factors and their receptors (FGFs and FGFRs) and T-box transcription factors (TBX), JAGGED1, Sonic Hedgehog, Patched, CREB-Binding Protein and many others. [12–18] FGF-FGFR signaling has been shown to be essential for normal facial morphogenesis through coordination of proliferation with bone morphogenetic protein.[18] There are a total of 22 FGF ligands in mammals, of which six and five are expressed in the mouse and chicken face, respectively, specifically in the superficial ectoderm surrounding the nasal slit and lining the mandibular cleft.[19–28]

FGFs bind to three FGF receptors in the facial mesenchyme. FGFR1 is ubiquitously expressed, while FGFR2 is expressed in the medial frontonasal mass mesenchyme and FGFR3 is restricted to the caudal edge of the frontonasal mass and medial edges of the maxillary prominences. [29,30] The essential role of FGF-FGFR signaling in facial morphogenesis is further evidenced in humans, where mutations in the *FGFR* genes lead to craniofacial malformations. One of these craniofacial malformations, craniosynostosis, the premature fusion of calvarial sutures, is associated with mutations in *FGFR* genes, as are the most common craniosynostosis syndromes. Interestingly, associated palatal anomalies including cleft palate and high arched palate have been described in many of these syndromes, including Pfeiffer syndrome (associated with mutations in *FGFR1* and *FGFR2*), Apert syndrome (*FGFR2*), Muenke syndrome (*FGFR3*) and Crouzon syndrome (*FGFR2*).[31–34] Palatal anomalies have also been reported in Saethre-Chotzen syndrome, a craniosynostosis syndrome associated with mutations in TWIST, which is an upstream modulator of FGF activity in cranial development.[35–39]

Of all of these craniosynostosis syndromes, Muenke syndrome is the most common, with an incidence of 1 in 30,000 births.[40] Muenke syndrome is an autosomal dominant craniosynostosis syndrome caused by a single defining gain of function point mutation in the

FGFR3 gene, c.749 C>G, which results in p.P250R (proline to arginine substitution at amino acid 250).[41] Individuals with Muenke syndrome typically have craniosynostosis most commonly involving the coronal suture (bilateral more often than unilateral), carpal and/or tarsal bone fusion, developmental delay, and sensorineural hearing loss.[42] Associated craniofacial anomalies include mild midfacial hypoplasia, high arched palate and hypertelorism.

Despite being the most common genetic cause of craniosynostosis, accounting for 24% of cases of craniosynostosis with an identified genetic cause, the frequency of oral and palatal anomalies including high arched palate, and cleft lip with or without cleft palate has not been documented in a patient series to date.[43] Further, cleft lip and palate has not yet been reported in a patient with Muenke syndrome, though one patient has been reported with isolated cleft palate.[34] In this investigation, we evaluate the frequency of palatal anomalies, midline anomalies and other oral findings in patients with Muenke syndrome through a retrospective investigation, as well as a literature review.

Materials and Methods

Retrospective chart review

A retrospective chart review was performed on patients with Muenke syndrome who had either been seen in person at the National Institutes of Health or had provided medical records as a part of our National Human Genome Research Institute/National Institutes of Health (Bethesda, MD, United States) IRB-approved protocol on Muenke syndrome from 2005–2011. In order to be included in this study, patients had to have documentation of the defining causative mutation of Muenke syndrome. Patients without documentation of this defining point mutation were excluded.

For patients who met the above criteria, the following data was collected and documented from the chart review: demographics: age, sex, date-of-birth and ethnicity, features of Muenke syndrome, craniosynostosis phenotype, findings on palatal exam, palatal anomalies, oral findings, midline defects, use of palate expander, medical history, surgical history, and auditory phenotype (including hearing loss, use of hearing aids and presence of recurrent otitis media).

Literature Review

A Medline search was conducted to find all previously reported cases of Muenke syndrome from 1996 (time period of intial description of Muenke syndrome) to the present (2011). The key words and patient terms searched included “Muenke syndrome,” “coronal synostosis,” “FGFR3craniosynostosis,” “P250R,” “Pro250Arg,” and “syndromic craniosynostosis.”

Papers included were those documented a palatal phenotype, that is the presence and/or absence of high arched palate, cleft lip and/or cleft palate and oral findings. Cases of Muenke syndrome were used from the following papers: [Abdel-Salam et al., 2010; Barbosa et al., 2008; Baynam et al., 2010; de Jong et al., 2011;Doherty et al., 2007; Escobar et al., 2009; Lowry et al., 2001; Muenke et al., 1997; Ranger et al., 2011; Reardon et al., 1997; Roscioli et al., 2001; Sabatino et al., 2004].Only cases with a documented p.P250Rmutation in FGFR3 were included. The palatal phenotype (documentation of palatal exam, presence or absence of high arched palate, cleft lip and/or cleft palate, oral findings) was recorded and tabulated.

Results

Retrospective chart review

A total of 21 patients who met the above criteria (documentation of defining Muenke syndrome *FGFR3* mutation) were included in this study. 16 of the 21 patients were seen in person at the National Institutes of Health in Bethesda, MD. For the 5 patients who were not seen in person at the NIH, available medical records were reviewed and medical histories with physical examination findings were provided by patients, family members and referring clinicians.

Eighteen patients (86%) had coronal craniosynostosis: 12 patients had bicoronal craniosynostosis, 6 patients had unicoronal craniosynostosis which was right-sided in 3 patients and left-sided in 3 patients (Table 1). The remaining three patients had macrocephaly. Hearing loss was present in all patients; 2 of these patients wore hearing aids. Sixteen patients (76%) had recurrent otitis media with effusion. Thirteen patients (62%) had documented familial inheritance/occurrence of Muenke syndrome, which was confirmed through genetic testing.

Sixteen patients (71%) had a structural anomaly of the palate (Table 2). Palatal findings included: high arched hard palate in 14 patients (67%); hard palate was high arched and narrow in 3 of these patients while 2 patients with a high arched palate had associated midline sagittal bony exostosis of the hard palate. One patient had torus palatinus, a term used to describe bony protrusion of the palate. Cleft lip and palate was present in one patient (5%). The patient with a cleft lip and palate in this study had a left cleft lip with involvement of the nasal septum, and a bifid hard and soft palate cleft. This patient had cleft lip repair at age four months with soft palate repair at 15 months and stage 2 palatoplasty at 21 months of age. Additional features of Muenke syndrome present in this patient were macrocephaly, sensorineural hearing loss (hearing aids since 2 years old), strabismus, and chronic otitis media.

There were no patients with isolated cleft lip or isolated cleft palate. 5 patients had additional defects associated with midline defects midline defects including cleft mitral valve and uvular deviation (n=1) (same patient with CLP), cervical spine fusion (n=1) and deviation of the nasal septum (n=4). 18 patients (86%) had oral findings, including dental malocclusion (n=10), crossbite (n=2), openbite (n=4)and dental crowding (n=5).

Discussion

Our study showed that 67% of patients with Muenke syndrome have a high arched palate. This corresponds with our literature review of palatal anomalies in patients with Muenke syndrome: of 763 patients with Muenke syndrome reported to date, 75 patients have had a documented palatal exam, 47 of these 75 patients (63%) were described as having a high arched palate (Table 3). Eleven of those forty-seven patients (23%) with a high arched palate had a palate that was described as high arched and narrow, a palatal finding that was present in 3 of our patients (21%).

Oral findings in patients described herein corresponded with oral findings described in patients with Muenke syndrome in the literature, commonly including dental crowding, malocclusion, crossbites, and openbites. This is most likely due to a combinatorial effect of a high arched palate and secondary effects of craniosynostosis on the skull, facial bones and dental architecture. In this study, two patients used palate expanders, which much success. This is an intervention to consider in patients with high arched palate, which can likely reduce the resultant effect of the high arched palate on dental crowding and malocclusion.

Of the 21 patients in our study, one patient had a cleft lip and palate (5%). Clefting of the lip and/or palate has been reported in only one prior patient with Muenke syndrome.[34] This patient had an isolated cleft palate. However, the extent of the cleft palate (complete vs. incomplete) and laterality were not described. Other features of Muenke syndrome in this patient included bicoronal craniosynostosis, developmental delay and intellectual disability.

Chronic otitis media occurs with a high frequency in patients with Muenke syndrome, thought to be secondary to the high arched palate which can cause intereference with the tensor veli palatini muscle, a muscle that functions in the opening and closing of the Eustachian tube. Otitis media with effusion also occurs with a high frequency in patients with cleft palate, due to aberrant attachment of the levator veli palatini leading to impaired ventilation of the middle ear. The patient in this study with cleft lip and palate had recurrent otitis media with effusion, which was likely at least partially due to the palatal cleft, as her palate was not highly arched. There may be yet unidentified factors in Muenke syndrome which contribute to the high frequency of recurrent otitis media that could contribute as well.

The incidence of cleft palate obtained both in our study (5%) and through our review of the literature (1.3%) is low relative to other forms of syndromic craniosynostoses in which cleft palate occurs, including Pfeiffer syndrome, Apert syndrome, Crouzon syndrome, and Saethre-Chotzen syndrome.[31–33,35] Stoler et al (2009) in studies of both Pfeiffer syndrome and Saethre-Chotzen syndrome, found an incidence of cleft palate of 8% and 6% respectively. In a series of 13 patients with Crouzon syndrome, 1 patient was noted to have clefting of the soft palate, particularly a bifid uvula (8%).[33] The highest incidence of cleft palate occurs in Apert syndrome, reported in 75% of patients in one series; cleft palate is associated more commonly with the p.S252W mutation in *FGFR2,* one of the 2 causative mutations of Apert syndrome, accounting for 66% of cases.[32] The other causative mutation of Apert, p.P253R in *FGFR2*, accounts for 33% of cases of Apert syndrome, and is associated with more severe syndactyly, thought to occur secondary to inappropriate autocrine activation of this particular mutant *FGFR2* gene specifically by the Fibroblast Growth Factor 10 (FGF10) ligand.[44.45]

All of the craniosynostosis syndromes associated with mutations in FGF signaling and upstream modulators of FGF signaling (Saethre Chotzen – *TWIST* gene) are associated with cleft palate. Further, cleft palate occurs more frequently in these syndromes when compared to the general population (0.05%).[46] Muenke syndrome is unique among these craniosynostosis syndromes, as it is defined by a single mutation in *FGFR3*, a gene involved in only one other craniosynostosis syndrome, Crouzon syndrome with acanthosis nigricans (also called “Crouzondodermoskeletal syndrome”). All other syndromic forms of craniosynostosis reflect extensive clinical description prior to gene discovery, and are associated with mutations. Even in this distinct scenario, where all patients with Muenke syndrome have the same point mutation in the same gene (*FGFR3),* there is a wide spectrum of clinical features and severity, due to the incomplete penetrance and variable expressivity of the mutation. It is not clear why some individuals with Muenke syndrome have cleft lip and/or palate while others do not. The most plausible explanation is the presence of secondary modifying factors, both environmental and genetic, which may affect the temperospatial expression patterns, and of the mutant FGFR3protein. The patient described herein with cleft lip and palate, represents a familial case of Muenke syndrome, with four affected individuals. However, she is the only member of her family with cleft lip and palate. This variable expressivity has also been demonstrated in identical twins with Muenke syndrome, who had vastly different features and clinical outcomes.[47]

A number of our patients had additional defects that involve midline structures, including a mitral valve cleft in the patient with cleft lip and palate, cervical spine fusion and nasal septal deviation. In the literature review, a patient with a high arched palate also had an atrial septal defect (ASD), ventricular septal defect (VSD), tracheosophageal fistula with esophageal atresia, and absence of the corpus callosum, all well known midline defects.

Individuals with Muenke syndrome have the lowest incidence of cleft palate among the most common craniosynostosis syndromes. However, the incidence of high arched palate in Muenke syndrome is quite high and may warrant clinical attention as these individuals are more susceptible to recurrent chronic otitis media with effusion and subsequent hearing loss and dental malocclusion. Historically, the care of individuals with syndromic craniosynostosis focused purely on correction of the skull defect. However, this and many additional studies have shown that these individuals have additional subtle but consequential anomalies, that also warrant clinical attention.

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Table 1

General Craniosynostosis and Auditory Phenotype of Muenke syndrome patient cohort
Total: 21 Patients
Familial cases:13 (62%)

Craniosynostosis Phenotype	Auditory Phenotype
Bicoronal Craniosynostosis: 12/21 (57%) Unicoronal Craniosynostosis: 6/21(29%) Right Sided: 3 Left Sided: 3 Macrocephaly: 3/21 (14%)	Hearing Loss: 21/21 (100%) Hearing Aids: 2/21 (10%) Recurrent Otitis Media w/Effusion: 16/21 (76%)

Table 2

Palatal, Midline and Oral Findings of Muenke syndrome cohort
Total: 21 Patients

Palatal Phenotype	Midline Defects	Oral Phenotype
Structural anomaly of the palate: 16/21 (76%) High arched palate: 14/21 (71%) - High arched and narrow palate: 3/15 - High arched palate with midline saggital bony exostosis:2/15 Torus palatinus: 1/21 (5%) Cleft lip and palate: 1/21 (5%)	Cleft Mitral Valve and Uvular Deviation: 1/21 (5%) Cervical Spine Fusion: 1/21 (5%) Deviation of the Nasal Septum: 4/21 (19%)	Dental malocclusion: 10/21 (48%) Crossbite: 2/21 (10%) Openbite: 4/21 (19%) Dental Crowding: 5/21 (24%) **Note: 3 patients had both dental malocclusion and a crossbite.*

Table 3

Literature Review of Palatal Anomalies in Muenke Syndrome

Total # Patients Reported with Muenke Syndrome	763
Total # Patients with Documented Palatal Exam	75
Palatal Anomalies • High Arched Palate • High Arched and Narrow Palate • Cleft Palate	48/75(64%) • 47/75 (63%) • 11/47 (23%) • 1/75 (1.3%)

Based on data from: Abdel-Salam et al., 2010; Barbosa et al., 2008; Baynam et al., 2010; de Jong et al., 2011;Doherty et al., 2007; Escobar et al., 2009; Lowry et al., 2001; Muenke et al., 1997; Ranger et al., 2011; Reardon et al., 1997; Roscioli et al., 2001; Sabatino et al., 2004