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Assessing the midface in Muenke syndrome: A cephalometric analysis and review of the literature☆

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Summary *Background:* Max Muenke included midface hypoplasia as part of the clinical syndrome caused by the Pro250Arg FGFR3 mutation that now bears his name. Murine models have demonstrated midface hypoplasia in homozygous recessive mice *only*, with heterozygotes having normal midfaces; as the majority of humans with the syndrome are heterozygotes, we investigated the incidence of midface hypoplasia in our institution's clinical cohort.
Methods: We retrospectively reviewed all patients with a genetic and clinical diagnosis of Muenke syndrome from 1990 to 2014. Review of clinical records and photographs included skeletal Angle Class, dental occlusion, and incidence of orthognathic intervention. Cephalometric evaluation of our patients was compared to the Eastman Standard Values.
Results: 18 patients met inclusion criteria — 7 females and 11 males, with average follow-up of 11.2 years (1.0—23.1). Cephalometric analysis revealed an average sella-nasion-A point angle (SNA) of 82.5 (67.8—88.8) and an average sella-nasion-B point angle (SNB) of 77.9 (59.6—84.1). The SNA of our cohort was found to be significantly different from the Eastman Standards ($p = 0.017$); subgroup analysis revealed that this was due to the mixed dentition group which had a higher than average SNA. 12 patients were noted to be in Class I occlusion, 4 in Class II malocclusion, and 2 in Class III malocclusion. Only one patient (6%) underwent orthognathic surgery for Class III malocclusion.

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Conclusions: While a part of the original description of Muenke syndrome, clinically significant midface hypoplasia is not a common feature. This data is important, as it allows more accurate counseling of patients and families.

Level of Evidence: III

Introduction

In 1997, Maximilian Muenke published his work outlining the discovery that a point mutation in the fibroblast growth factor receptor 3 (FGFR3) gene on chromosome 4p results in the clinical findings today referred to as Muenke Syndrome.[1] His description at that time included bilateral or unilateral coronal synostosis, midface hypoplasia, downslanting palpebral fissures, sensorineural hearing loss, developmental delay, ptosis, and a number of radiographic and clinical abnormalities of the hands and feet. Muenke syndrome has now been widely accepted as one of the major forms of syndromic craniosynostosis. Several attempts have been made in the literature to characterize the phenotypic variability and many patients who had previously been either undiagnosed or misdiagnosed have been reclassified as having Muenke Syndrome.[2–8,17]

One aspect of the clinical presentation of Muenke syndrome that continues to be variably characterized in the literature is midface hypoplasia. There are several articles that depict it as a consistent finding, and others that report a complete absence of the pathology.[9] Laboratory studies assessing the pathophysiological basis of Muenke syndrome in a murine model have also reported consistent midface hypoplasia.[10,11] However, in our clinical practice, we observed relatively normal mid-facial growth in most patients with Muenke syndrome (Figure 1). As such, the goal of this study was to use our institutional experience to cephalometrically analyze the midface of our patients with Muenke syndrome for a more definitive characterization that would allow for improved and more consistent diagnosis.

Methods

All patients who have presented to the Craniofacial Clinic at the Children's Hospital of Philadelphia with an eventual diagnosis of Muenke Syndrome from 1990 to 2014 were identified. Inclusion criteria mandated genetic confirmation of the FGFR3 Pro250Arg genetic mutation, a complete medical chart, photographs, and X-ray or CT imaging with a digitally reproduced lateral cephalogram of adequate quality for cephalometric evaluation. All standard X-ray lateral cephalograms were obtained with the patient in the natural head position, while CT images were obtained with the patient in the supine position and the neck neutral between flexion and extension. While there is no consensus on the gold standard imaging modality in cephalometric analysis, it has been found that fair comparisons can be made between these two imaging modalities, specifically in regards to angular measurements within the same tomographic plane.[12]

With our institutional review board's approval, patients' medical records were retrospectively reviewed. Photographs and clinical records including patient demographics, age at initial presentation, length of follow up, Angle's class of dental occlusion, and incidence of orthognathic intervention were all documented. Cephalometric analysis was performed to measure the angle between the sella turcica, the nasion, and points A (SNA) and B (SNB). For both SNA and SNB angles, the sella-nasion represents the reference line. The A-point is the point at the deepest concavity on the anterior curvature of the maxilla, while the B-point is the corresponding point on the mandible. Consequently, the SNA captures the horizontal position of the maxilla in relation to the cranial base, while the SNB indicates the horizontal position of the mandible in relation to the cranial base. Cephalometric measurements of our

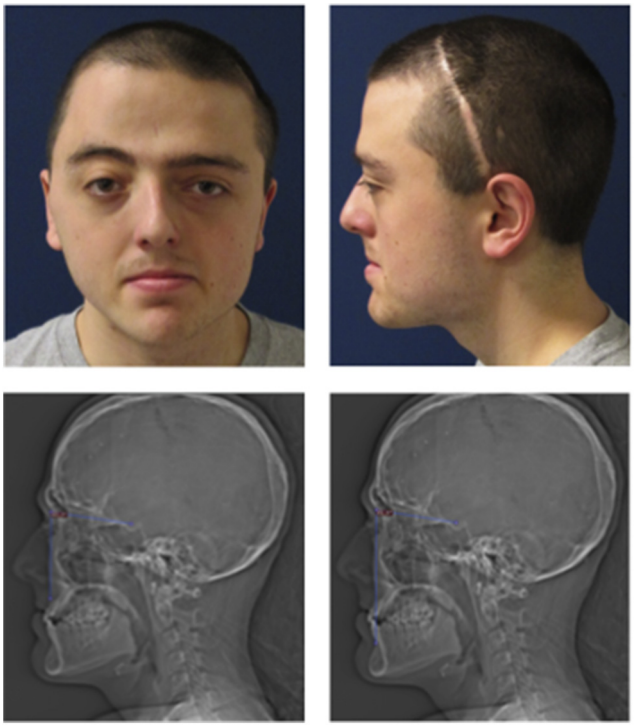

Figure 1 AP/lateral and cephalometric measurements of a patient with Muenke syndrome demonstrating normal SNA/SNB angles and a lack of clinically significant midface hypoplasia.