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Review Article

Hearing loss in syndromic craniosynostoses: Otologic manifestations and clinical findings

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ABSTRACT

Objective: This review addresses hearing loss as it occurs and has been reported in Muenke syndrome as well as six additional *FGFR* related craniosynostosis syndromes (Apert syndrome, Pfeiffer syndrome, Crouzon syndrome, Beare-Stevenson syndrome, Crouzon syndrome with acanthosis nigricans, and Jackson-Weiss syndrome.
Data sources: Pub-Med, Medline, Cochrane Database, Science Direct, NLM Catalog.
Review methods: A Medline search was conducted to find all reported cases of the 7 FGFR related syndromic craniosynostosis. Special attention was paid to literature that reported hearing findings and the audiology literature.
Results: Hearing loss occurs in variable percentage as a component part of all FGFR related craniosynostosis syndromes. Our literature review revealed the following incidences of hearing loss in FGFR craniosynostoses: 61% in Muenke syndrome, 80% in Apert Syndrome, 92% in Pfeiffer syndrome, 74% in Crouzon syndrome, 68% in Jackson Weiss syndrome, 4% in Beare Stevenson syndrome and 14% in Crouzon syndrome with Acanthosis Nigricans. The majority of the hearing loss is a conductive hearing loss, with the exception of Muenke syndrome where the majority of patients have a sensorineural hearing loss and Crouzon syndrome where almost half of patients have a pure or component of sensorineural hearing loss.
Conclusion: This manuscript presents a diagnostic and management algorithm for patients with syndromic craniosynostosis. It will aid clinicians in treating these patients and further, the recognition of a possible syndrome in patients with hearing loss who also have syndromic features.
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1. Introduction

Craniosynostosis is the premature fusion of one or more of the calvarial sutures. Changes in the displacement and curvature of the skull bones during development are necessary to allow the brain to expand, and sutures normally remain patent during growth [1]. Premature fusion leads to abnormal growth patterns resulting in alterations in cranial and facial morphology [2]. The precise extent and nature of the resultant head shape alterations depend on which sutures fuse prematurely, the order in which they fuse, and when during development, this developmental aberration occurs. Craniosynostosis has an incidence of approximately 1 in 3000 live births [3]. Craniosynostosis may occur in an isolated form, without additional anomalies, or it may occur with additional anomalies, as part of a syndrome. To date, there are over 180 identified forms of syndromic craniosynostosis. The most common syndromic forms of craniosynostosis are associated with mutations in the *FGFR* genes [4]. There are 7 clinically distinct craniosynostosis syndromes that result from mutations in the three *Fibroblast Growth Factor Receptor* (*FGFR)* genes (*FGFR1, FGFR2, FGFR3*). Among the FGFR related craniosynostosis syndromes are Muenke syndrome, Apert syndrome, Pfeiffer syndrome, Crouzon syndrome, Beare Stevenson syndrome, Crouzon syndrome with acanthosis nigricans (also called "Crouzonodermoskeletal syndrome") and Jackson-Weiss syndrome (Figs. 1–4 and Table 1) [3]. All of these syndromes clinically are characterized by craniosynostosis which involves the coronal suture in the majority of patients. An exception is Muenke syndrome where patients have variable craniosynostosis. They are also characterized by hearing loss, and additional anomalies which vary per syndrome (for example syndactyly in Apert syndrome tarsal/metatarsal coalitions in Jackson-Weiss syndrome, proptosis in Crouzon syndrome and deviated halluces in Pfeiffer syndrome) (Table 1). All of these syndromes are characterized by mutations in one of the 3 *FGFR* genes. Detailed descriptions of features that are unique to each syndrome are below.

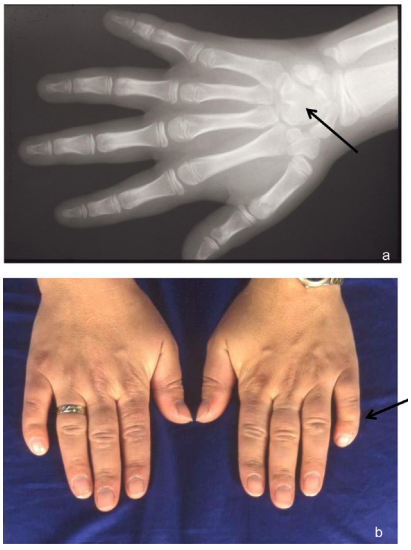

Fig. 1. (a) Carpal bone fusion (capitate-hamate) in a patient with Muenke syndrome (black arrow). (b) Broad thumbs and clinodactyly in a patient with Muenke syndrome (black arrow).

Fibroblast growth factors (FGFs) bind to three FGF receptors in the facial mesenchyme. The FGFRs transduce extracellular signals from the fibroblast growth factors to the cytoplasm [5]. The FGFRs are modulators of bone and connective tissue growth. 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 [6,7]. 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. The mutations that occur in craniosynostosis are activating mutations thus leading to excessive deposition of bone and thus, the premature closure of the calvarial sutures that normally should remain patent as the brain grows.

2. Methods

2.1. Literature review

A search was conducted to find previously reported cases of the FGFR related craniosynostosis from the first description of the earliest defined syndrome to the present (2013). The following databases were used: PubMed, NLM Catalog, Science Direct and the Cochrane Database. Inclusion criteria were: articles with confirmed diagnosis of one of the seven craniosynostosis syndromes (clinical diagnosis was accepted for all syndromes except Muenke syndrome where articles without molecular genetic diagnosis were excluded) and articles with audiological and/or otologic focus.

3. Results

3.1. Muenke syndrome

Muenke syndrome is an autosomal dominant craniosynostosis syndrome characterized by unilateral or bilateral coronal craniosynostosis, hearing loss, intellectual disability and relatively subtle limb findings such as carpal and/or tarsal bone fusion (Fig. 1). Muenke syndrome is caused by a single defining point mutation in the *Fibroblast Growth Factor Receptor (FGFR3)* gene. A total of 763 patients with Muenke syndrome were ascertained from the literature. The presence or absence of hearing loss was clearly documented in 262 patients (34%), of which 160 were reported to have hearing loss (61%). Of the 160 patients with hearing loss, 126 patients had a purely sensorineural hearing loss (79%). Hearing loss was conductive in 14 patients (9%), mixed in 8 patients (5%) and not specified in the remainder of patients (Tables 2 and 3).