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Craniofacial and extracraniofacial anomalies in craniofacial microsomia: A multicenter study of 755 patients

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ABSTRACT

Purpose: Craniofacial microsomia (CFM) is a congenital malformation of structures derived from the first and second pharyngeal arches leading to underdevelopment of the face. However, besides the craniofacial underdevelopment, extracraniofacial anomalies including cardiac, renal and skeletal malformation have been described. The aim of this study is to analyse a large population of patients with regard to demographics, typical phenotypes including craniofacial and extracraniofacial anomalies, and the correlations between the different variables of this condition.

Material and methods: A retrospective study was conducted in patients diagnosed with CFM with available clinical and/or radiographic images. All charts were reviewed for information on demographic, radiographic and diagnostic criteria. The presence of cleft lip/palate and extracraniofacial anomalies were noted. Pearson correlation tests and principal component analysis was performed on the phenotypic variables.

Results: A total of 755 patients were included. The male-to-female ratio and right-to-left ratio were both 1.2:1. A correlation was found among Pruzansky–Kaban, orbit and soft tissue. Similar correlations were found between ear and nerve. There was no strong correlation between phenotype and extracraniofacial anomalies. Nevertheless, extracraniofacial anomalies were more frequently seen than in the 'normal' population. Patients with bilateral involvement had a more severe phenotype and a higher incidence of extracraniofacial and cleft lip/palate.

Conclusion: Outcomes were similar to those of other smaller cohorts. Structures derived from the first pharyngeal arch and the second pharyngeal arch were correlated with degree of severity. Extracraniofacial anomalies were positively correlated with CFM. The findings show that bilaterally affected patients are more severely affected and should be approached more comprehensively.

1. Introduction

Craniofacial microsomia (CFM) is generally considered to be the second most common congenital craniofacial malformation following cleft lip and palate (Grabb, 1965; Poswillo, 1988). Goldenhar characterized the disorder as a triad of accessory tragus, mandibular hypoplasia and epibulbar dermoid (Goldenhar, 1952). Later, the disorder was called 'otomandibular dysostosis' and 'first

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and second branchial arch syndrome' (Francois and Haustrate, 1954; Stark and Saunders, 1962). Gorlin et al. called this condition 'oculo-auriculo-vertebral syndrome' (OAVS), a term often found in genetics literature (Gorlin et al., 1963). However, in the surgical field, CFM is nowadays most often used.

Any structure derived from the first and second pharyngeal arches can be affected, leading to a phenotype predominantly characterized by asymmetrical hypoplasia of the facial skeleton. Although several theories have been proposed, the exact aetiology has not yet been clarified. The well-known hypotheses are local haemorrhage of the stapedial artery (Poswillo, 1975) and disturbed migration of cranial neural crest cells (Johnston and Bronsky, 1995; Tuin et al., 2015), leading to asymmetrical development of structures derived from the first and second pharyngeal arches (Stark and Saunders, 1962; Converse et al., 1973).

The first pharyngeal arch gives rise to the mandible, maxilla, zygoma, trigeminal nerve, muscles of mastication, and a part of the external ear, whereas the second pharyngeal arch gives rise to the facial nerve, stapes, styloid process, portions of the hyoid bone, facial musculature, and the majority of the external ear (Moore, 2011). CFM is most often regarded as a unilateral malformation; however the facial structures have been reported to be involved bilaterally in 10% of cases (Ross, 1975; Posnick et al., 2004). Previous studies suggested that, in most cases, the contralateral side is abnormal as well, although not truly hypoplastic (Ongkosuwito et al., 2013).

Patients with CFM are phenotypically heterogeneous; their dysmorphologies range from minor to severe. Therefore, a comprehensive classification is needed to describe the severity of the different anomalies to ensure clear communication among physicians in various specialties and researchers. The Pruzansky classification was the first such system, which was later subcategorized by Kaban et al (Pruzansky, 1969; Kaban et al., 1986). This schema focuses only on mandibular hypoplasia. The Orbit, Mandible, Ear, Nerve, Soft tissue (O.M.E.N.S.), proposed by Vento et al., includes the five major malformations in craniofacial regions (Vento et al., 1991).

Other anomalies seen in patients with CFM include malformations of the vertebrae, cervical spine, cardiorespiratory system, urogenital system, limbs, central nervous system and gastrointestinal system. Most often reported are skeletal, cardiac and renal anomalies (Heike et al., 1993).

To encompass the extracraniofacial anomalies, the acronym was expanded to the O.M.E.N.S-plus (Horgan et al., 1995). The most recent derivative of the O.M.E.N.S-plus is the pictorial Phenotypic Assessment Tool-Craniofacial Microsomia (PAT-CFM) by Birgfeld et al. (2011). The PAT-CFM also includes scoring of both the mandible on radiography as on medical photography, cleft lip, macrostomia and an additional detailed assessment of minor deformities such as epibulbar dermoids and skin and ear tags.

Several studies provided insight into the aetiology, prognosis and treatment of CFM by assessment of correlations between the degree of mandibular hypoplasia and the other anatomic variables in the O.M.E.N.S.-plus (Rollnick et al., 1987; Vento et al., 1991; Horgan et al., 1995; Poon et al., 2003; Barisic et al., 2014; Park et al., 2014; Tuin et al., 2015). A correlation between the degree of mandibular hypoplasia and the other anatomic dysmorphologies is observed in all studies, especially the correlation between the degree of mandibular hypoplasia and orbital deformity (Vento et al., 1991; Poon et al., 2003; Barisic et al., 2014; Park et al., 2014; Tuin et al., 2015). Tuin et al. concluded that structures derived from the first pharyngeal arch are associated in degree of severity, as are the structures derived mainly from the second pharyngeal arch (Tuin et al., 2015). Furthermore, there are studies of possible association between the O.M.E.N.S score and the likelihood of coexistent extracraniofacial anomalies (Rollnick et al., 1987; Vento et al., 1991; Horgan et al., 1995; Poon et al., 2003; Barisic et al., 2014; Park et al., 2014; Tuin et al., 2015).

None of the previous studies on this topic used principal component analysis (PCA) to correlate multiple variables at the same time. PCA is a way to reduce the data description into a smaller amount of relevant variables, without reduction of the data themselves (Jongman et al., 1987; Nieuwboer et al., 1998; Jolliffe 2002).

Previous studies on this condition, included a relatively small number of patients, varying from 65 to 100. One exception is an analysis of 259 patients; however, this study documented the prevalence of OAVS at birth. These numbers might explain the differences in distribution of the O.M.E.N.S. score and the reported correlations and associations (Rollnick et al., 1987; Vento et al., 1991; Horgan et al., 1995; Poon et al., 2003; Barisic et al., 2014; Park et al., 2014; Tuin et al., 2015). To study a large group of patients with CFM, we initiated a multicenter collaboration including the craniofacial units of Rotterdam, London and Boston.

The aim of this study is to analyse the largest population of patients with CFM with regard to severity, laterality and gender ratio as well as possible correlations among the different components of the PAT-CFM, including cleft lip and palate, and extracraniofacial anomalies. Furthermore, we investigated whether certain combinations of anomalies occur more frequently than others by using PCA, which might provide more insight into the embryologic processes that cause CFM.

2. Materials and methods

This retrospective study was conducted in a population diagnosed with CFM at the Craniofacial Units of Erasmus MC, Rotterdam, The Netherlands; Great Ormond Street Hospital in London, UK; and Boston Children's Hospital in Boston, Massachusetts, USA. This study was approved by the Institutional Review Boards (Rotterdam: MEC-2013-575; London: 14 DS25; Boston: X05-08-058).

We identified patients diagnosed with CFM presented at one of the units from January 1980 until January 2016. Patients were included only if medical photography and/or radiography of the face and medical history were available. Patients with isolated microtia, i.e., without mandibular hypoplasia on radiologic images, and patients diagnosed with other craniofacial syndromes that include craniofacial hypoplasia (e.g., Treacher Collins syndrome) were excluded. All charts were reviewed for information on demographic, radiographic and diagnostic criteria.

The severity of the deformity was scored in patients with the help of O.M.E.N.S.-plus or PAT-CFM. The orbit (O) is based on the size and position: scores ranging from O0 to O4. The mandible was scored on both, photography (M0-M3) and radiography (Pruzansky–Kaban Type I–Type III). Type I mandibles are smaller in size with normal dimensions and position of the condyle and ramus. Type IIA mandibles are smaller in size with decreased overall dimensions, but normal position, of the condyle and ramus. Type IIB mandibles are smaller in size with decreased overall dimensions of the condyle and ramus, furthermore the temporomandibular joint (TMJ) is malformed and displaced. In the Type III mandible, the ramus, condyle and TMJ are absent. External auricular anomalies are graded from E0 to E4, i.e., normal ear to anotia. Facial nerve weakness is categorized from N0 to N4. Soft tissue deficiency varied from normal soft tissues, SO, to severe soft tissue deficiency, S3.

There were few records with photography that depicted facial nerve paresis (N0-N4); therefore, facial nerve function was taken from the chart or was not included. According to PAT-CFM, both a global and detailed assessment, i.e., cleft lip/palate, ophthalmic anomalies and presence of ear and/or skin tags, were performed