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Systematic Review
Craniofacial Anomalies

Central nervous system anomalies in craniofacial microsomia: a systematic review

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Abstract. Extracraniofacial anomalies, including central nervous system (CNS) anomalies, may occur in craniofacial microsomia (CFM). This systematic review was performed to provide an overview of the literature on the prevalence and types of CNS anomalies and developmental disorders in CFM, in order to improve the recognition and possible treatment of these anomalies. A systematic search was conducted and data on the number of patients, patient characteristics, type and prevalence of CNS anomalies or developmental delay, and correlations between CFM and CNS anomalies were extracted. Sixteen papers were included; 11 of these described developmental disorders. The most common reported anomalies were neural tube defects, corpus callosum agenesis or hypoplasia, intracranial lipoma, Arnold–Chiari malformations, hydrocephaly, ventriculomegaly, and cerebral hypoplasia. The prevalence of CNS anomalies in CFM varied from 2% to 69%. The prevalence of developmental disorders, such as intellectual disability, language or speech developmental delay, and neuropsychomotor delay, varied from 8% to 73%. This study suggests that CNS anomalies and developmental disorders are seen in a substantial proportion of patients with CFM. Further research should focus on determining which features of CFM are correlated with CNS anomalies to allow adequate screening and timely care.

Key words: craniofacial microsomia; oculo-auriculo-vertebral syndrome; hemifacial microsomia; Goldenhar; central nervous system; developmental disorder; systematic review.

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Craniofacial microsomia (CFM) is a heterogeneous congenital disorder with an incidence of 1:3000 to 1:5000 live births[1–4]. CFM results in unilateral or bilateral underdevelopment of the structures formed by the first and second branchial arches. The mandible, maxilla, zygoma, ear, facial soft tissues and musculature, and the facial nerve may be affected[1,5,6]. Although some familial cases of CFM are described in the literature and several genes have been associated with this disorder, the aetiology of CFM remains unknown[4,7–10]. The most conventional theory is that CFM is the result of a disturbance in the development of the first and second branchial arches during the first 6 weeks, causing the facial

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malformations typical of CFM[11–13]. CFM is a clinical diagnosis and the dysmorphology of CFM ranges from mild to severe. Isolated microtia might be a minor form of CFM, but it is generally not regarded as CFM[3,6,12].

The OMENS classification is most often used to grade craniofacial malformations in CFM patients[14]. Extracraniofacial anomalies can be present in CFM and occur in different organ systems including the central nervous system (CNS) and skeletal, renal, heart, lung, and gastrointestinal organs[12–19]. Therefore, the OMENS-Plus classification was created to document the presence of associated extracraniofacial anomalies[19]. Over the years, several terms have been used for CFM including hemifacial microsomia (HFM), Goldenhar syndrome, oculo-auriculo-vertebral dysplasia or spectrum, lateral facial dysplasia, and first and second branchial arch syndrome[5,20–23].

The presence of CNS anomalies in CFM is well documented. There are a variety of anomalies and these may or may not cause symptoms. Epilepsy, motor disabilities, or developmental disorders may occur[24–27]; these may be the result of a CNS anomaly, but are often non-specific[26].

The aim of this review was to document the prevalence and types of CNS anomalies and developmental disorders in patients with CFM, in order for them to be recognized and possibly treated early.

Methods

Search strategy

This study was guided by the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) statement[28]. A systematic search of the literature was performed to identify papers focusing on CFM and its synonyms, combined with synonyms for CNS and spinal anomalies. Since the spinal cord is part of the CNS and is embedded in the vertebral column, synonyms for spinal anomalies were incorporated into the search to identify all papers regarding CNS anomalies. The search was conducted in Embase, MEDLINE in Ovid, Cochrane Central, Web of Science, PubMed (articles not yet indexed in MEDLINE), and Google Scholar (most relevant articles) from inception until 21 June 2016. Results were limited to human subjects and studies written in the English language. No date limits were applied, but conference abstracts, letters, notes, and editorials were excluded. See the **Supplementary Material** online for the full search strategies of all databases.

Two researchers (R.W.R. and C.J.J.M.C.) selected the studies independently. Titles and abstracts were screened for relevance based on the inclusion and exclusion criteria. Studies concerning CFM in relation to CNS anomalies were further examined. Studies were included when the type and/or prevalence of CNS anomalies or developmental disorders in CFM were mentioned. Only original studies were included. Case reports and studies describing solely patients with isolated microtia were excluded. However, data concerning the CFM patients were extracted from papers describing both patients with isolated microtia and CFM.

Data extraction

A table with predetermined characteristics was made prior to full-text review of the papers. All studies were graded on quality of evidence using the Oxford Centre for Evidence-Based Medicine (CEBM) criteria. Data on the number of patients, inclusion criteria of the studies, types of CNS anomaly, prevalence of CNS anomalies in CFM, and other correlations between CFM and CNS anomalies were extracted when available.

Results

Study selection

The flowchart of the literature search is presented in Fig. 1. Of the 3646 papers screened on title and abstract, 3630 records were excluded for being irrelevant. Sixteen studies were included for qualitative data analysis. Ten studies described both CNS anomalies and developmental disorders, one study described solely developmental disorders, and five studies described only CNS anomalies in CFM.

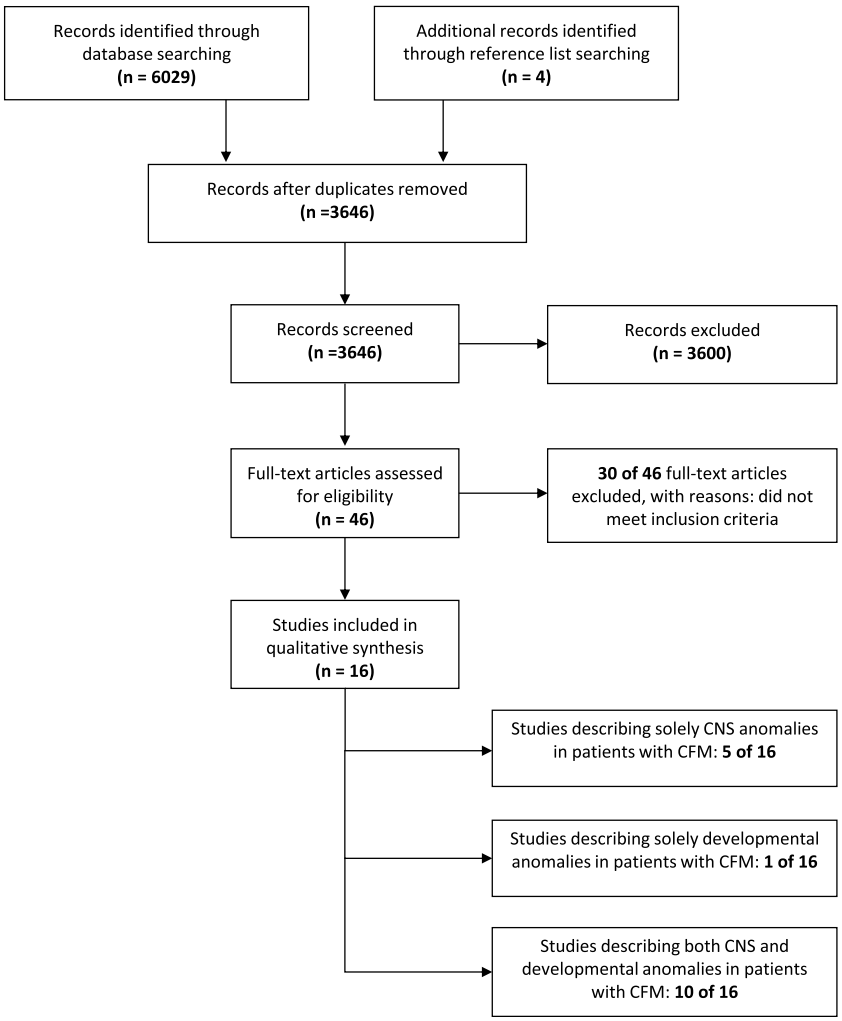

Fig. 1. PRISMA diagram of the systematic review methodology.