CRANIOFACIAL MICROSOMIA

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List of abbreviations:

CFM	Craniofacial microsomia
HFM	Hemifacial microsomia
GS	Goldenhar syndrome
TMJ	Temporomandibular joint
OSA	Obstructive sleep apnoea
CNS	Central nervous system
MDO	Mandibular distraction osteogenesis
OAVS	Oculoauriculovertebral syndrome

1.INTRODUCTION:

CFM is one of the main terms used to describe the congenital abnormality characterized by underdeveloped facial features arising from the first and second branchial arches. Other terms used to describe such a condition include hemifacial microsomia (HFM), first and second branchial arch syndrome, Goldenhar syndrome (GS), otomandibular dysostosis and oculoauriculovertebral syndrome. (1) (2) In 1989, Cohen et al (3) came up with the term oculoauriculovertebral spectrum to include all of the different phenotypical variations that can be seen in this condition. Even though there is no definite diagnostic criteria for CFM, affected patients will all suffer from some degree of hypoplasia affecting the facial tissues namely skeletal and soft tissue, ear, orbit and facial nerve. (4)

2.EPIDEMIOLOGY:

CFM is the second most common facial anomaly after cleft lip and palate. It is most often quoted as affecting between 1 in 3500 to 1 in 5600 newborns in the United States but this may be an underestimate because there is no clear-cut criteria for diagnosis of this condition. For reasons that are idiopathic, the disorder is 50% more prevalent in males than in females. Most cases are unilateral (85%) with the right side being affected the most in a 3:2 ratio. (5)(6)(7) According to EUROCAT data, congenital defects of the ear, face and neck including CFM have a prevalence of 1.53 per 10,000 births per year in Malta. (8)

3.EMBRYOLOGY

During the 4th week of gestation, neural crest cells from the neural tube migrate to branchial arches, which are a series of five paired swellings of mesenchyme. These branchial arches are made up of ectoderm, mesoderm and endoderm and will give rise to the various structures making up the face. The first and second branchial arches are those associated with CFM.

They give rise to skeletal, muscular, vascular and neural structures innervated by trigeminal (cranial nerve V) for the first pharyngeal arch and the facial nerve (cranial nerve VII) for the second pharyngeal arch. The first arch consists of the mandibular and maxillary processes, which give rise to structures associated mostly with the oral jaw including the maxilla, mandible, zygoma, trigeminal nerve, muscles of mastication, malleolus of incus and the anterior portion of ear. The second arch consists of the hyoid arch which gives rise to structures associated mainly with jaw support, including the hyoid bone, stylus process, facial nerves and muscles, most of the ear and stapes. (7) For these structures to form, cell-to-cell communication must be maintained. Disruption of such a communication may result in hypoplasia or aplasia of the affected structure. (9)

4.1.PATHOGENESIS/AETIOLOGY:

CFM has a multifactorial type of inheritance with both intrinsic and extrinsic causes. There are three leading hypotheses explaining the aetiology of CFM.

4.1.1.VASCULAR EROSION OF THE STAPEDIAL ARTERY

The stapedial artery maintains blood flow between the first and second branchial arches. (7) In 1973, Poswillo (10) conducted a series of experiments on mice where he administered triazine, a teratogen in the 6th week of gestation. This caused a haematoma in the stapedial artery leading to a hypoxic environment and as a result caused a disruption in communication between the two pharyngeal arches. This vascular insult created phenotypes which are similar to those observed in CFM. Furthermore, the different degrees of occlusion in the artery could be the reason behind the wide range of phenotypes that exist.

4.1.2.ABNORMAL DEVELOPMENT OF MECKEL'S CARTILAGE

In 1992, Cousley and Wilson (11) developed a hypothesis which stated that hemifacial microsomia (HFM) could be a result of abnormal development of Meckel's cartilage. Meckel's cartilage develops from the first branchial arch and forms the cartilaginous part of the mandibular arch and therefore, provides a sort of scaffold for normal lower jaw development. It is also associated with middle ear formation. Since abnormalities of the middle ear and lower jaw are associated with HFM, it was hypothesized that interference by vascular events of Meckel's cartilage could be the cause of HFM.

4.1.3.ABNORMAL DIFFERENTIATION, MIGRATION OR DEATH OF NEURAL CREST CELLS

Neural crest cells play an extremely important role in craniofacial development. Their migration from the neural tube to the pharyngeal arches is necessary for the normal formation of facial structures. Thus, abnormal development, death or abnormal migration of these cells can lead to CFM. (12)

These three pathogenic models are interrelated with each other. Meckel's cartilage is derived from neural crest cells and any vascular insult can disrupt neural crest cell or Meckel's cartilage development. Likewise, anomalies in neural crest cells may lead to abnormal blood flow in the craniofacial area. Therefore, these three hypotheses may interact with each other to produce the HFM phenotype. (13)

4.2.ENVIRONMENTAL FACTORS:

There are numerous environmental factors which may be responsible for the pathogenic models. Risk factors include teratogen exposure such as thalidomide, vasoactive drug use such as ibuprofen, gestational smoking, second trimester vaginal bleeding, multiple gestation, the use of assisted reproductive technology as well as maternal diabetes mellitus. Such risk factors may lead to the disruption in embryonic blood flow for example, a local haemorrhage in stapedial artery which can lead to a hypoxic environment and damage to surrounding tissues. (14) (15)

4.3.GENETICS

Whilst most cases seem to be sporadic with no previous family history, growing evidence suggests that there is a genetic predisposition. Previously it was believed that only 2% of cases have a familial history however, this is probably an underestimate since some mild cases may have gone undiagnosed or misdiagnosed. (5) A later study by Kaye and colleagues (16) has suggested that up to 44% of cases have a familial basis with a recurrence rate of 2-3% in first degree relatives. Data has suggested an autosomal dominant inheritance with incomplete penetrance for this congenital anomaly.

Research has indicated many possible chromosomal abnormalities that are responsible for HFM. The main pathogenic genes often quoted in literature are summarized in Table 1. Causes such as 5p deletions, duplication of 14q23.1 and abnormalities of chromosomes 18 and 22 have been frequently implicated as causes of CFM. (17)

Table 1 showing the main pathogenic genes associated with CFM

Gene/s	Position on chromosome	Type of mutation
Crkl	22q11.2	Deletion (18) (19) (20) (21)
OTX2, SIX6, SIX1	14q22.3	Duplication (22)
NXD2, IRX4, IRX2	5p15.33-pter	Deletion (23)
GSC	14q32	Deletion (24)
OTX2	14q23.1	Duplication (25) (26)

5.PRESENTATION AND DIAGNOSIS:

CFM is generally diagnosed clinically however, radiographic tests such as MRI, CT scans, panoramic radiography and TC3D as well as genetic tests for possible pathogenic genes and mutations can aid in confirming the diagnosis. (27)

Throughout the scientific community there still seems to be no agreement on the establishment of clear and specific diagnostic criteria for CFM. However, many clinicians suggest that hypoplasia of one or more structures arising from the first and second branchial arches is required for diagnosis of CFM. In 1993, Cousley (28) proposed the following minimum diagnostic criteria:

1. Homolateral lower jaw and ear defects
2. Asymmetrical mandibular and auricle defects together with
    a. Two or more secondarily related abnormalities
    b. Positive familial history of CFM

5.1.CLASSIFICATION SYSTEMS:

The heterogenic nature of the disease presentation led to the creation of many classification systems. These classification systems proved to be useful in determining the course of action after diagnosis since the treatment and surgical plan depends on the severity of the deformity.

The first accepted classification system for CFM was proposed by Pruzansky (29) in 1969 where he concentrated on the underdevelopment of the mandible. Based on radiographic findings he grouped mandibular hypoplasia into three possible presentations. In 1988, Kaban and colleagues (30) added on this system by also describing the position of the temporomandibular joint (TMJ).

Later on, classification systems which described and included all the parts of the face were formulated. In 1987, the SAT system was developed by David and colleagues (31) to include skeletal, auricular and soft tissue abnormalities. This classification system was further modified by Vento and colleagues (32) in 1991 to create the OMENS (Orbit, mandible, ear, nerve, soft tissue) classification system and later on was termed OMENS+ by Horgan et al (33) in 1995 to include other abnormalities apart from those affecting the craniofacial region.

The latter is probably the most widely accepted classification system used by physicians for CFM. It includes all the possible craniofacial defects such as orbital deformation, underdevelopment of the mandible, auricular defects, nerve and soft tissue defects. The OMENS system uses a scoring system where each section is scored between 0 and 3 with 3 being the most severe. In a total deformity score, the greater the score, the greater the severity of the CFM phenotype. A visual representation of the OMENS+ was created in 2007 (34) and later adjusted in 2011(35) so as to try to standardize diagnosis of CFM.

6.CLINICAL MANIFESTATIONS:

CFM has a wide phenotypic presentation with a broad spectrum of manifestations usually associated with structures originating from the first and second branchial arches. While some cases may present with just some mild facial asymmetry and so are quite easy to miss, other cases may be very severe with gross facial asymmetry, microtia and extracranial presentations such as cardiac and renal problems. The main clinical presentations observed in CFM are summarized in Table 2.

Table 2 Clinical manifestations of CFM according to the system affected(36)

System affected	Feature/s and clinical manifestations
Ocular	• Upper eyelid colobomas • Epibulbar dermoids • Anophthalmia/microphthalmia • Orbital dystopia
Auricular and auditory	• Microtia • Anotia • External auditory canal atresia • Pharyngotympanic tube dysfunction • Preauricular skin tags • Conductive hearing loss
Maxillofacial and oral region	• Mandibular asymmetry - hypoplastic jaw, agenesis of condyle and ramus, aplasia of TMJ • Underdeveloped muscles of mastication • Delayed dental development and hypodontia • Malocclusion • Macrostomia • Feeding difficulties
Neurologic	• Facial nerve palsy • Sensorineural hearing loss • Impaired extraocular movements • Asymmetrical palatal elevation
Respiratory	• Upper airway obstruction • Obstructive sleep apnoea (OSA)
Cardiac	• Tetralogy of Fallot • Septal defects • Situs inversus

Renal	• Renal agenesis • Double ureter • Hydronephrosis • Hydroureter • Crossed renal ectopia
Vertebral	• Hemivertebrae • Scoliosis • Fusion of vertebrae • Occipitalization of atlas • Spina bifida • Compression of brain and spinal cord • Cervical spine instability
CNS	• Neural tube defects • Corpus callosum agenesis or hypoplasia • Intracranial lipomas • Hydrocephaly • Microcephaly • Arnold-Chiari malformation • Ventriculomegaly • Cerebral hypoplasia
Developmental	• Speech and language delay • Neuropsychomotor delay • Intellectual disability • Social problems

7.MANAGEMENT:

Since CFM is an abnormality which presents with a wide array of phenotypic presentations, the treatment plan of such a condition should be tailored personally to each patient. No single surgical protocol exists and the management plan should be adapted according to the patients' age and severity of abnormalities. (7) Developing a sustainable and long-term treatment plan is not an easy task and should be done within a multi-disciplinary team since the condition affects almost all functional aspects of life including breathing, communication, feeding, growth, speech, development and quality of life. (37) An overview of a treatment plan according to the different life-stages is summarized in Table 3.

Table 3 Overview of evaluations and treatments in CFM patients according to life-stage

Life Stage	Evaluations	Common surgeries/treatments
Antenatal	• Prenatal diagnosis using ultrasound • Polyhydramnios	• Preparation of the neonate team for life-threatening emergencies immediately after birth
Neonate	• Respiratory status • Renal and cardiac consultations • Assess facial asymmetry • Oral health	• Airway procedures eg. tracheostomy • Cardiac and renal corrective surgeries if life-threatening • Eyelid colobomas repair
Infancy and early childhood	• Hearing status • Feeding and growth • Assess facial asymmetry • Oral health	• Removal of preauricular skin tags • Cleft lip/palate and gross macrostomia repair • Hearing augmentation (hearing aids) • Eye drops and eye bandaging if facial nerve palsy present • Mandibular distraction osteogenesis (MDO) or costochondral grafting in cases where there is respiratory compromise due to craniofacial malformation • Removal of lipodermoids and epibulbar choristomas
Mixed dentition stage (6-12 years)	• Obstructive sleep apnoea (OSA) and airway problems • Psychosocial aspects • Orthopaedic consultation • Assess facial asymmetry • Occlusion • Oral health	• Ear reconstruction – autologous or alloplastic • Facial reanimation surgery/tarsorrhaphy • Mandibular and maxillary surgery to fix hypoplastic mandible through: • Orthodontic appliances • Costochondral grafts to reconstruct the temporomandibular joint (TMJ) and condyle-ramus unit • MDO • Aural atresia repair • Soft tissue augmentation using fat grafts or vas

Adolescence and adulthood	• OSA symptoms • Psychosocial health • Oral health • Occlusion	• Corrections and retouching of previous surgeries and secondary defects

8.FUTURE WORK:

Further research is required to comprehend better the molecular mechanisms of CFM so that the exact pathogenesis of CFM is elicited. Small-molecule drugs as well as CRISPR/CAS9-based genome editing are two potential preventative and treatment measures that however, require plenty of more research and studies. (13)

9.CONCLUSION:

CFM is a term used to describe the congenital anomaly associated with hypoplasia of facial structures originating from the 1st and 2nd branchial arches. It is documented as being one of the most common craniofacial anomalies with a broad spectrum of phenotypical presentations and different degrees of severity. The aetiology of CFM is multifactorial with environmental and genetic causes. Due to differences in severity between patients suffering from CFM, clinicians created classification systems so as to better classify CFM patients making it easier to develop a standardized plan of action depending on patient class. Since clinical manifestations are not limited only to the craniofacial area, the best treatment plan should take a holistic approach within a multidisciplinary team that will cater to the patient's needs throughout his or her life.

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