CLASSIFICATION AND MANAGEMENT OF HEMIFACIAL MICROsomia: A LITERATURE REVIEW

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ABSTRACT

Hemifacial microsomia (HFM) is the 2nd most common craniofacial birth defect after cleft lip and palate. It is said to arise from the 1st & 2nd intrauterine branchial arches. HFM is believed by many experts to be congenital but not inherited as most patients afflicted have no previous family history. It is also known as craniofacial microstomia with cranial involvement. The real cause is unknown but largely blamed on hemorrhage of the stapaedial artery. The phenotypic expression is variable from mild to severe involving many structures such as bone, nerve, muscular tissues and soft tissue. Facial structures commonly affected include the ears, the mouth and the mandible. Mostly unilateral but bilateral have been reported. However, not much is known about this condition in sub-Saharan Africa. Multidisciplinary team management is the general consensus for optimal care. Awareness in sub-Saharan Africa of this disorder is still evolving

This review identifies various classifications, diagnoses, investigations, treatment and timelines for management of HFM. The aim of the current review was to discuss the diverse controversies, classification, diagnosis and treatment of HFM so as to increase the understanding of this condition.

Keywords: Congenital malformation, Syndrome, Hemifacial microsomia, Hypoplasia, Classification, Distraction osteogenesis, Orthognathic surgery

INTRODUCTION

Hemifacial microsomia (HFM) is among over 250 congenital syndromes that cause asymmetrical anomalies of derivatives of the first and second brachial arches. In 1881, Carl Ferdinand Von Arlt, a German physician was the first to describe this malformation. It has attracted sizeable attention in the literature over several decades resulting in conflicting names such as brachial arch syndrome, lateral facial dysplasia, oto-mandibular dystosis and first and second brachial arch syndrome. Many authors used to consider Goldenhar syndrome as a different entity from HFM until current evidence proved that it is actually a variant of HFM. Goldenhar syndrome which Gorlin and associates formerly referred to as oculo-auriculo-vertebra dysplasia/spectrum is also associated with cardiac and renal defects in addition to vertebral malformation and epibulbar dermoids. ‘Craniofacial microsomia’ as coined by Converse and associates involves the presence of cranial defects with other characteristic features of HFM.

According to several studies across the globe, HFM is the second most common congenital craniofacial birth defect after cleft of the lip and palate. (1989) put the incidence of this anomaly as 1 in every 5600 newborn. However, recent finding of a higher figure of 1 in 3000 have been reported. Predilection for males with a male-female ratio of 3:2 has been demonstrated by many investigators. HFM occurs sporadically with most people affected possessing no positive family history of this deformity; hence, there is strong consensus that it is genetic but not hereditary.

The genetic basis of HFM is just gradually being unraveled. A recent study in 2018 by Chen and associates found mutation in large host of genes such as OTX2, PLCD3 and MYT1 in people with HFM. Coincidentally, HFM is associated with about 7% to 15% of both typical cleft lip/palate and Tessier’s atypical facial cleft. Similar environmental factors and teratogens like maternal diabetes and thalidomide, retinoic acid, triazene, vasoactive medications have been blamed for the occurrence of HFM.

Nevertheless, the controversies persistently engulf the aetiopathogenesis of HFM with three models proposed. Experimenting in animals, Poswillo declared that following administration of 10mg/kg of thalidomide to female pregnant mice; resultant hemorrhage from rupture of stapaedial artery led to
complete damage or partial disruption of the development of the first and second brachial arches and localized necrosis of their derivatives.\textsuperscript{11,12} The others are the abnormal development of the cranial neural crest cells and Merkel’s cartilage due to damage or destruction by teratogens.\textsuperscript{10,11,12} Although, Chen and colleagues advocated that the first theory is the most plausible of the lot.\textsuperscript{10} However, they insisted that these three mechanisms might have acted in concert during the first 9–8 weeks of gestation to cause the derangements that produce the numerous related features of HFM.\textsuperscript{13}

Phenotypic expressions of HFM depend on the extent of this haemorrhage and its effect on these two arches.\textsuperscript{11,12,13} Therefore, there is a wide spectrum of presentation of this malformation varying from the mild to the severe spanning the skeletal, neural, muscular tissues and soft tissue. It affects the development of the lower half of the face, most commonly the ears, the mouth and the mandible.\textsuperscript{6,8,9,13} There is an assortment of degrees and combinations of underdevelopment and malformations of this region.\textsuperscript{6} Several reports observed usual occurrence on one side of the face, but involvement of both sides have been shown.\textsuperscript{6,11,13} However, there is paucity of research and knowledge about this complex malformation in Nigeria and the sub-Saharan Africa.

The purpose of this current article is to review the literature and summarize pertinent information about the aetiopathogenesis, classification, clinical presentation, radiological investigations, differential diagnosis and surgical treatment of hemifacial microsomia.

**MATERIALS AND METHODS**

An electronic search of the literature was performed in PUBMED and google scholar without time restriction for appropriate English papers on hemifacial microsomia based on a series of keywords in different combinations: “craniofacial microsomia”, “oto-mandibular dysostosis”, “auriculo-oculo-vertebra spectrum”, “Goldenhar syndrome”, “lateral facial dysplasia”, “first and second brachial arch syndrome”, “OMEN”, “distraction osteogenesis”, “maxilla”, “mandible”, “treatment”, “Kaban and Pruzansky”, and “classification”. Prospective, retrospective studies, randomized/nonrandomized clinical trials, meta analysis, cohort studies, case–control studies, and case reports were considered. The reference lists of original and review articles were also sought. In addition, a manual exploration of major oral and maxillofacial surgery textbook was undertaken. Letters to the Editor, historical reviews, and unpublished articles were excluded.

**RESULTS**

**Aetiology**

This multifactorial aetiogenesis can be divided into genetic and environmental factors.\textsuperscript{6,13}

**Genetics**

Continuing research have confirmed the complex genetic mosaic in HFM and demonstrated the constellation of genes involved.\textsuperscript{10} X-linked, autosomal dominant and recessive patterns have been discovered in familial cases of HFM. Mutations in OTX2, PLCD3 and MYT1 genes have recently been discovered to play a crucial role in the aetiopathogenesis of HFM.\textsuperscript{1,2,3,10,13} In addition, previous genetic studies implicated chromosomal deletion in trisomy 18, 5q and duplication in 7q in HFM.\textsuperscript{5,10,13} It was observed that HFM is common with children born through assisted reproduction in the USA.\textsuperscript{13,14} The age of the parents and donor might be a cofounder in this situation.\textsuperscript{13,14,15} However, there are ongoing attempts to shed more on the exact molecular processes and understand the pathogenesis of HFM through whole gene sequencing in animals and large clinical studies.\textsuperscript{10}

<table>
<thead>
<tr>
<th>Grade I</th>
<th>Smaller mandible than the preserved normal side</th>
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<tr>
<td>Grade II</td>
<td>on the affected mandible; condyle, ramus, and sigmoid notch identifiable, but grossly distorted in size and shape</td>
</tr>
<tr>
<td>Grade III</td>
<td>affected mandible is grossly distorted, loss or agenesis of ramus, condyle and TMJ.</td>
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**Environmental Factors**

Drugs and chemicals such as retinoic acid, triazene, primidone, thalidomide exposure; and use of vasoactive medications have been revealed to be strong risk factors in the aetiology of HFM. Several mothers with diabetes in developed countries have been reported to give birth to HFM children.\textsuperscript{2,3,4,14}

**Pathogenesis**

It is aetiologically and pathogenetically heterogeneous.\textsuperscript{6,10,13} The pathogenesis of HFM remains highly controversial with three plausible mechanisms suggested.\textsuperscript{10,13} Poswillo through his observations in the classic experiment in pregnant mice postulated that thalidomide induce vascular damage with consequent haemorrhage of the stapaedial artery and the resultant haematoma consequently impedes the development of first and second brachial arches.\textsuperscript{16} He stated that the bigger the haematoma and the longer it takes to

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resolve, the more complex and severe the anomalies are. Johnston and Bronsky contradicted these theories with their proposition that teratogenic effect on neural crest cells cause the abnormal development and migration of neural crest cells between 30 and 45 days of gestation. They argued this occurred before the thalidomide induced damage which affects only the second brachial arch. The third hypothesis is the damage to merkel’s cartilage with possible retarding factor on the development of these two brachial arches contributing to the occurrence of HFM. Chen and associates, however, assert that the most plausible construct is the first. Pathogenesis of HFM still remains an enigma as many leading researchers in this field conceded that none of the above models fully explained the many variable features of HFM and overlapping characteristic with syndromes like Treacher-Collins, Down and DiGeorge.

Classification of HFM
In order to most favorably manage HFM numerous classifications have been developed based on the anatomic and diverse clinical presentations, thus, helping to construct an optimal treatment plan. An extensively adopted and widely applied system for HFM in clinical use was first pioneered by Samuel Pruzansky in 1969 (Table 1). He used simple plain posterior-anterior radiographic view of the jaw to grade the affected mandible into three distinct morphologies.

This classification stood for nearly two decades until Kaban and colleagues (1988) utilized teleradiography to modify and increase the earlier classification into four groups based on the TMJ anatomical status. Grade II was further divided into a and b, (Table 2).

<table>
<thead>
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<th>Table 2: Kaban et al. classification of HFM</th>
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<tr>
<td>Type I Normal mandible-Type I</td>
</tr>
<tr>
<td>Type IIA The mandible and glenoid fossa are small-Type IIA Short ramus, glenoid fossa is in an anatomically acceptable position</td>
</tr>
<tr>
<td>Type II B Short ramus, TMJ is inferiorly, medially and anteriorly displaced with hypoplastic condyle</td>
</tr>
<tr>
<td>Type III Complete absence of ramus, glenoid fossa and TMJ</td>
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<th>Table 3: OMENS classification for HFM</th>
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<tr>
<td><strong>A. Orbit</strong></td>
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<tr>
<td>O0 Normal</td>
</tr>
<tr>
<td>O1 Small size</td>
</tr>
<tr>
<td>O2 Poor position</td>
</tr>
<tr>
<td>O3 Both small size and poor position</td>
</tr>
<tr>
<td><strong>B. Mandible (and TMJ)</strong></td>
</tr>
<tr>
<td>M0 Normal mandible-Type I</td>
</tr>
<tr>
<td>M1 The mandible and glenoid fossa are small-Type IIA</td>
</tr>
<tr>
<td>M2A Short ramus, glenoid fossa is in an anatomically acceptable position-type IIA</td>
</tr>
<tr>
<td>M2B Short ramus, TMJ is inferiorly, medially and anteriorly displaced with hypoplastic condyle-Type II B</td>
</tr>
<tr>
<td>M3 Complete absence of ramus, glenoid fossa and TMJ-Type III</td>
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<tr>
<td><strong>C. Ear</strong></td>
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<tr>
<td>Ear anomaly can be classified into external, middle/atresia and presence of branchial arch remnants/sinus tracts.</td>
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<tr>
<td>Max and Meurmen’s system is used in OMENS</td>
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<tr>
<td>E0- normal ear</td>
</tr>
<tr>
<td>E1- mild hypoplasia and cupping with all structures present</td>
</tr>
<tr>
<td>E2- absence of external auditory meatus with variable hypoplasia of the concha</td>
</tr>
<tr>
<td>E3-malposition lobule with absent auricle</td>
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<tr>
<td><strong>D. Facial nerve-fourth cranial nerve</strong></td>
</tr>
<tr>
<td>N0 No facial nerve involvement</td>
</tr>
<tr>
<td>N1 Upper facial nerve involvement (temporal zygomatic)</td>
</tr>
<tr>
<td>N2 Lower facial nerve involvement (buccal, mandibular, cervical)</td>
</tr>
<tr>
<td>N3 All branches of facial nerve affected</td>
</tr>
<tr>
<td>N.B Hypoglossal (N12) and trigeminal (N3) nerves can also be affected.</td>
</tr>
<tr>
<td><strong>E. Soft tissue deficiencies</strong></td>
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<tr>
<td>S0 normal-No obvious soft tissue or muscle deficiency</td>
</tr>
<tr>
<td>S1 mild-Minimal subcutaneous/muscle deficiency</td>
</tr>
<tr>
<td>S2 Moderate–between the two extremes S1 and S3</td>
</tr>
<tr>
<td>S3 Severe soft tissue deficiency due to subcutaneous and muscular hypoplasia</td>
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</table>
Following advancement in medical knowledge and better understanding of the complexities and multisystem nature of this condition, Vento and associates (1999) proposed a more expansive classification called by the acronym ‘OMENS’ which mirrors UICC ‘TNM’ system in classification of cancers.\textsuperscript{23} (Table 3) This while overcoming the deficiency of earlier classifications of Pruzansky and Kabans’ fixation on the mandible. The ‘OMENS’ acronym include O-Orbit, M-Mandible, E-Ear, N-Nerve and S-Soft tissue. Series of amendments were subsequently made to this classification between 1995 and 2007 to accommodate the discovery of extracranial structures with + added to the OMENS, now OMENS+ and pictorial form to facilitate standardization, transmission, teaching and research. The pictorial form of OMENS+ was further modified in 2011.\textsuperscript{21} However, most commentators have expressed misgivings on the laborious and time consuming demands of this classification but admitted the immense advantage of the clinical thoroughness especially for easier and methodical treatment planning.\textsuperscript{6,13}

Unlike its predecessors, a new classification for HFM known as craniofacial deformity scoring (CFDS) has failed to galvanize broad acceptability since its introduction in 2001.\textsuperscript{6} It is a combination of mandibular scoring deformity and cranial deformity scoring totaling 16 and 19 points for each respectively with heavy reliance on computer tomography to analyze each different bone structures has been found to be challenging with a huge learning curve.\textsuperscript{15}

**Clinical Presentation**

The clinical features of HFM are broad spectrum and vary from one individual to the other. Previous works shows that due to its complex and random expression there is a large range of phenotypic appearance which depends on the constellations of the host genes involved.\textsuperscript{6,8,13}

Often, the disorder has been found to be unilateral but few report observed that the condition do present bilaterally with the characteristic asymmetry of the cranio-maxillofacial complex.

The more commonly affected structures include ear (external and midle which result in conduction defects between 30-50%), mandible [ascending ramus, condyle and temporomandibular joint (TMJ)], orbit, zygomatic arch and maxilla. Soft tissues majorly involved include facial nerve and muscles such as masseter and temporalis.\textsuperscript{6,11,12,13}

This unevenness of the mandible and TMJ result in serious dental consequences such as malocclusion, impaction, delayed eruption, noticeable jaw deviation to the uninvolved side with sometimes presence of ankylosis and velopharyngeal insufficiency.\textsuperscript{5,12}

The positioning of the orbit might be altered (orbital dystopia) with presence of dermoids (epibulbar), retinal or choroidal coloboma, blepharoptosis, microphthalmia or anophthalmia and others.\textsuperscript{6,8,13}

Some patients could also present with absent ear (anotia), small ear (microtia), disorders of the middle ear and very bad cases with hearing loss.\textsuperscript{6,8,9} Furthermore, the seventh (facial) cranial is frequently affected with different degrees of affection of the upper or lower branches and in severe cases the fifth (trigeminal) and twelfth (hypoglossal) cranial nerves could also be vulnerable.\textsuperscript{6,13}

In addition, findings of abnormal teeth development and eruption such as dental hypoplasia, agenesis, microdontia, malocclusion and delayed teeth eruption have been demonstrated.

Extracranial structures such as kidney, central nervous system (CNS), gastrointestinal tract (GIT), heart, lungs and skeletal could be affected in severe cases.\textsuperscript{6,9,13} Hence, the classification of HFM is indispensable to optimally correct and restore the anatomic parts involved to full function.\textsuperscript{6}

**Imaging for HFM**

Plain radiographs of the skull have been generally exploited in the diagnosis of HFM.\textsuperscript{6,13} With recent advancement in radiology, advanced imaging tools like cone beam computed tomography (CBCT), spiral multi-slice computed tomography (MSCT), Magnetic resonance imaging (MRI), ultrasound (USS) and three dimensional surgical stimulation models like stereolithographics are gaining popularity.\textsuperscript{6,8,9,22}

Three-D device like stereolithographies has helped to revolutionize the treatment of HFM while simultaneously surmounting the problem of insufficient evaluation and quantification of soft and bony tissues by customary 2-dimension imaging techniques. It also makes pre-operative virtual surgical planning easier with customization of the necessary implants needed to restore the deficient areas.\textsuperscript{3,13,22} Cassi and colleague reported the increased use of noninvasive, non-ionizing radiation devise such as laser surface scanner, stereophotogrammetry or ultrasonographic measurements to quantify facial proportion and topography in HFM.\textsuperscript{8}

Computer-guided surgical planning and simulation due to increase accuracy, facilitates surgical procedure,
shortens operation time, makes customization of reconstruction plate easier and minimizes complications compared to conventional approach to surgical planning. It is widely utilized by advanced centres in western countries and north Africa.\textsuperscript{6,8,13} However, the high cost of this technology is sadly out of reach of many centres in developing nations.

**Differential Diagnosis**

This includes hemimandibular hypoplasia in which there is no soft tissue deficiency, presence of glenoid cavity but chin deviation due to condylar, coronoid and ramus hypoplasia.\textsuperscript{6,13} Syndromes such as Treacher-collins, CHARGE, Parry Romberg, Miller-Dierker, cranio-oto-renal, Townes-Brooks and many others that have similarity with HFM. Therefore, a geneticist needs to rule them out.\textsuperscript{6,8,13,24,25} Pertinently, bilateral presentation of HFM can easily be misdiagnosed as Treacher-Collins but the distinguishing features is that the one side would be more asymmetrical with or without one side slanted than the other. This is in contrast to the almost mirror image of the hypoplasia in both side of the face in Treacher-Collins in addition to micrognathia.\textsuperscript{13}

**Clinical Presentation**

The clinical features of this anomaly vary considerably but commonest dominator is the facial asymmetry associated with mandibular hypoplasia and TMJ incongruity.\textsuperscript{8,13} This is majorly unilateral but occasionally can be bilateral. Maxillary/zygomatic hypoplasia, external/internal ear abnormalities/ataxia, coloboma, parotid hypoplasia and microphthalmia.\textsuperscript{10,11} There are also several dental derangements such as oligodontia, malocclusion, open bite and delay eruption. Other congenital anomalies that might be present include vertebral anomalies, cardiac defects, renal defects, mental retardation and host of other soft tissue disorders.\textsuperscript{12,13}

**Team Management**

Previous studies have consistently documented the importance of multidisciplinary approach in the proper management of HFM. This team is inclusive of large arrays of health professionals spanning paediatric surgery, medicine, dental and other allied fields.\textsuperscript{6,8,13} Plastic/maxillofacial surgeons, orthodontists, paedodontists, restorative/prosthetic dentist and periodontologists are the major specialists involved in achieving optimal corrective aesthetic, functional restoration of normal occlusion and TMJ function.\textsuperscript{8,23} Some workers also highlight the importance of other experts like the cardiothoracic surgeon, orthopaedic/spine surgeons, geneticists and neurosurgeon.\textsuperscript{6,8,9,13,24,25} Unfortunately, in Africa only few countries in northern and southern Africa are able to provide this cohort as it is commonly found in Asian, Europe and other developed nations.\textsuperscript{8,25,26}

**Treatment**

Treatment to correct the dental, skeletal and soft tissues anomalies in HFM can start from childhood even unto early adulthood.\textsuperscript{6,23,24,25} Treatments of these disabilities are in phases and can be split into surgical and non-surgical.\textsuperscript{8,9,13} According to Cassi et al surgical treatment of HFM patients depend on the extent and severity of deformity with repair of bony, soft tissues and specialized organs like the ear and nerves.\textsuperscript{8}

**Timing of Surgery**

Regarding the timing of surgery there are two rival schools of thought with one advocating that this disorder is not progressive and any major surgical intervention should be delayed until after puberty.\textsuperscript{24,25} This they advance would ensure stable and predictable treatment outcome with minimal need for revision surgery; and less health care burden on the family and health system. The divergent view vehemently assert that it is needless to wait for skeletal maturity before commencing surgical intervention as this congenital anomaly is progressive and would get worse over time if early treatment is not instituted.\textsuperscript{26,27} They also underline the necessity to circumvent the serious psycho-social cost of stigmatization to the child and family; and to diminish the burden of care on the health system. Many longitudinal studies buttressed the position of the former.\textsuperscript{25}

Although few data supports the second point of view with their findings being disputed as a result of short period of follow up.\textsuperscript{26,27} However, recent outcome studies established that the results in both approaches are comparable in terms of outcome and long lasting stability.\textsuperscript{24} An investigator, on the other hand, extols the successful integration of the two approaches in their craniofacial centre.\textsuperscript{13}

**Reconstructive Options**

There are arrays of surgical procedures to restore bony loss and soft tissues in HFM which include vascularized and non-vascularized tissue flaps, prosthetic implants, distraction osteogenesis and orthognathic surgery.\textsuperscript{6,27,28} There has been controversy whether orthognathic surgery was superior to distraction osteogenesis.\textsuperscript{6,8,13,29} Although for Kaban I and IIA anomalies distraction osteogenesis have achieved some limited success.\textsuperscript{6,12,13} Orthognathic surgery with or without bone grafting is more favoured by surgeons in its ease of wider application.\textsuperscript{6,13,29} A recent meta-analysis, nevertheless, concluded that both were comparable in terms of rate of recurrence and surgical outcome.\textsuperscript{29}
In Kaban IIB and III with underdeveloped bone and missing TMJ, TMJ reconstructions with costochondral graft were often put into regular use. Sternoclavicular, iliac and fibula bones have also been used to successfully reconstruct the TMJ. In richer climes of Europe and America, total TMJ replacement with expensive titanium implant have found acceptance by both patients and surgeon alike. Total ear reconstruction with cartilage from the rib has also attracted tremendous attention in the surgical community. Nerve graft from the sural nerve have also been effectively utilized to reconstruct the facial nerve in patients.

Non-Surgical Treatment

However, removable functional orthodontic appliances like Andresen, Frankel appliance and asymmetrical functional activator (AFA) (hybrid of bite block components of the bionator and the vestibular shield. Being employed in early childhood to treat the mandibular deficiency in mild Kaban’s type II A. The disadvantages of this measure are that it is laborious and requires patient’s steadfastness and cooperation in order to achieve tangible results.

Early orthopedic intervention in childhood have been observed to improve aesthetics, function, and reduce psychological trauma and obviate the need for maxillary and mandibular osteotomies in late adolescence. Although some authors have reported successful correction of facial asymmetry in type I and IIa HFM children with functional appliances. Long-term follow up showed that some of these children eventually require orthognathic surgery to correct the skeletal and dental malocclusion.

CONCLUSION

In summary, HFM is a complex malformation affecting principally the craniomaxillofacial region. Its pathogenesis is still not well defined and presents with a wide variation of clinical characteristics that affects both hard and soft tissue. Huge resources and long term multidisciplinary team approach are required for optimal management. Surgical and non-surgical treatments have been effectively deployed to achieve optimal aesthetic and functional outcomes.

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