

## Minireview Article

### HEMIFACIAL MICROSOMIA : A MINI REVIEW

**ABSTRACT:** Hemifacial Microsomia (HFM) is a rare congenital anomaly involving embryological derivatives of the first and second branchial arches and characterized mainly by mandibular hypoplasia and unilateral or bilateral microtia; although, other facial structures may be affected. It may have long-term effects on psychological development and social well-being, due to unaesthetic facial appearance, functional disturbances and complex medical treatments.

**Key words:** hemifacial microsomia (HFM), omens classification, facial asymmetry/hypoplasia.

#### INTRODUCTION

Hemifacial microsomia (HFM) is a variable, complex developmental malformation of the body involving asymmetrical hypoplasia of the face and ear. It is a rare congenital anomaly that involves immature derivatives from the first and second pharyngeal arches characterized by mandibular underdevelopment and unilateral or bilateral microtia; although, other facial structures may be affected. Disordered craniofacial development frequently results in definitive facial asymmetries that can significantly impact an individual's social and functional well-being.

#### INCIDENCE AND NOMENCLATURE: HEMIFACIAL MICROSOMIA.

HFM is a common facial anomaly or birth defect involving the first and second BA structures and ranks second in prevalence only behind facial clefting/ cleft lip and palate.<sup>1</sup> It is estimated that three percent of all newborns have significant facial structural anomalies<sup>2</sup>. Another incidence study report as 1 of 3500 births, yet there has been little research on its risk factors and sequelae<sup>3</sup>.

Nomenclatures such as first and second arch syndrome, Oral-mandibular-auricular syndrome, Oculoauriculovertebral dysplasia (OAV) and Goldenhar syndrome, lateral facial dysplasia, unilateral craniofacial microsomia, otomandibular dysostosis have been applied to HFM assuming different etiologies for cases with or without epibulbar dermoid and/or vertebral anomalies. However, it is now understood that these various combinations of vertebral anomalies with HFM represent gradations in the severity of a similar morphogenic error.<sup>4,5,6</sup>

HFM is defective formation of first and second branchial arches during development of face hence the nomenclature- first and second arch syndrome. Goldenhar first described the triad of epibulbar dermoids or choristomas, preauricular skin appendages, and pretragal blind-ending fistulas in association with mandibular facial dysplasia.<sup>7</sup> Later patients with associated vertebral anomalies were given the classification of Oculoauriculovertebral dysplasia (OAV) dysplasia.<sup>8</sup> However the diagnostic criteria of Goldenhar syndrome remain unclear, thereby making clinical use of the term "Goldenhar" inconsequential and it was over diagnosed subjectively in patients who show more severe HFM features.<sup>9</sup> When the features of the OAV complex are

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40 predominantly unilateral and lack vertebral anomalies and epibulbar dermoids, the condition has been called  
41 Hemifacial microsomia (HFM). This pattern is thought to represent a variant of the expanded OAV complex.

42 MM Jr, Rollnick BR, Kaye CI. Oculoauriculovertebral spectrum: an updated critique. *Cleft Palate J*  
43 1989;26:276–86.

**Comment [U2]:** If they are references, enter the number

44 There is increasing evidence that hemifacial microsomia (HFM), Goldenhar syndrome (GS), and  
45 oculoauriculovertebral dysplasia (OAV) are part of a spectrum within a single entity. Frequency of cervical  
46 spine malformations in HFM and microsomia was greater than values for a normal population and this further  
47 supports the probable association between HFM, GS, and OAV.<sup>10</sup>

This reference has been deleted in the revised article. A revised article is attached for your kind consideration.

#### 48 **ETIOPATHOGENESIS:**

49 The etiopathogenesis of this developmental disorder can be discussed in terms of its embryologic development -  
50 - that causes hypoplasia of structures derived from the first and second branchial arches during the first six  
51 weeks of gestation.<sup>11,12</sup> Since the mandible plays a prominent role in defining symmetry of face and, act as an  
52 active region of growth, so it commonly acquires asymmetric features.<sup>13</sup> HFM risk of an individual is related to  
53 maternal exposures affecting blood flow to particular fetal tissues and suggested that maternal use of vasoactive  
54 medications in the first trimester and associated cigarette smoking. The risk is also studied using DNA  
55 collection and it showed that genetic variation is possible in pathways associated with vasculogenesis and  
56 hemostasis. Additional risk factors of HFM that might represent vascular events include multiple gestations,  
57 diabetes, 2nd trimester bleeding, and heavy alcohol consumption by the mother.<sup>3</sup>

58 Since the knowledge of the genetic basis of human disease and its effect on embryologic development has  
59 greatly expanded in recent years. HFM are generally thought to result from a combination of inadequate  
60 migration and formation of facial mesenchyma. Because many structures of the head and neck migrate during  
61 fetal development, an understanding of embryologic development helps determine the origin and nature of such  
62 congenital lesions.<sup>14</sup>

63 Poswillo suggested that hematoma might be involved in the development of HFM in rodents and primates.<sup>15</sup> A  
64 study suggested that hematoma at the site of the developing stapedia artery and mandibular hypoplasia were  
65 observed among the offspring of CS1 mice treated with triazene during gestation. Also a similar hemorrhagic  
66 pattern was observed among *Macaca irus* monkeys treated with thalidomide in pregnancy; minor developmental  
67 delays of the condyle and middle ear primordia were also noticed. There are clinical evidences suggesting  
68 reduced carotid flow on the affected side of HFM cases; further raising the possibility that HFM might result  
69 from a vascular disruption pathogenesis.<sup>16,17</sup> Thus HFM encompasses a broad spectrum of phenotypes  
70 resulting from defective development of the first and second pharyngeal arch structures and associated with  
71 anomalies of the mandible and other facial bones, ears, and overlying soft tissues. The cause of HFM is thought  
72 to involve both extrinsic and genetic risk factors.<sup>18</sup>

73 Two or more anomalies may be interrelated with a similar etiopathologic link, suggesting an overlapping  
74 pathogenesis. Whether the cause is genetic or environmental, there may be a common pathway leading to a  
75 disturbance in neural crest cell migration in HFM who also have a concurrent cleft lip or palate.<sup>19</sup>

#### 76 **GENETICS AND HEMIFACIAL MICROSOMIA:**

77 There is evidence that genetics play an important role in non-Mendelian-inherited type of HFM and  
78 concordance has been reported for both monozygotic and dizygotic twins, but the high level of discordance in  
79 monozygotic twins suggests that both genetic and environmental factors are important for the manifestation of  
80 this disorder. Based on families with inherited forms of HFM, the patterns of occurrence of both HFM and  
81 isolated microtia have suggested that either an autosomal recessive or autosomal dominant inheritance pattern is  
82 likely in such developmental anomalies.<sup>20,21,22</sup> It has been shown that HFM can be induced genetically through a

83 mouse chromosome 10 mutation, although a gene has not yet been identified and sometimes there is no family  
84 history of HFM in most of the cases.<sup>23</sup>

## 85 **PSYCHOLOGICAL STATUS IN HEMIFACIAL MICROSOMIA**

86 The psychological impact of the disorder hinders the overall growth of the individual with HFM. The affected  
87 children are more inhibited, depressed, anxious, and introverted, and less socially adaptable.<sup>24</sup> They may have  
88 poor academic performance, peer rejection and higher levels of internalizing behavior problems than children  
89 unaffected by such craniofacial abnormalities.<sup>3</sup>

90 Studies and further analyses will determine whether they vary by HFM phenotype, parenting style, or other  
91 indicators of social risk (e.g., level of education or socioeconomic status). Sometimes, neuropsychological  
92 development may be more directly compromised by underlying major or minor central nervous system  
93 malformations associated with some cases of HFM.<sup>25</sup>

## 94 **CLASSIFICATION OF HEMIFACIAL MICROSOMIA**

95 Numerous classification systems have been devised to facilitate the individualized components of this complex  
96 condition and spectrum of disease.<sup>26</sup> Several other classification systems have been developed to help stratify  
97 patients based on the severity of their defects.<sup>18</sup>

98 One of the most recent classification systems, the OMENS system, scores five clinical manifestations of  
99 hemifacial microsomia according to dysmorphic severity on a scale from 0 to 3: orbital asymmetry, mandibular  
100 hypoplasia, ear deformity, nerve dysfunction, and soft-tissue deficiency. The OMENS classification represents  
101 the most comprehensive, versatile, objective, and easily adaptable attempt at clinical classification of HFM to  
102 date. The authors also propose a concise clinical evaluation form using a modified version of the system to  
103 promote the use of the OMENS system, to aid in the evaluation of hemifacial microsomia patients, and also to  
104 assist in data sharing amongst clinicians and surgeons.<sup>27</sup> The terms and systems of classification have been  
105 reviewed multiples times but OMENS (orbit, mandible, ear, cranial nerve, and soft tissues) system has been  
106 proposed to classify the severity of each of the major craniofacial manifestations of HFM. There is often a  
107 unilateral deformity of the external ear. A coloboma of the upper eyelid is frequently encountered and may be  
108 seen radiographically on soft-tissue windows. Ear deformities range from isolated preauricular tags to atresia of  
109 the external auditory canal (EAC). A detailed examination of the temporal bone should be performed to  
110 evaluate associated, though uncommon, malformations of the middle ear and an aberrant course of the facial  
111 nerve.<sup>6</sup>

## 112 **CLINICAL MANIFESTATIONS:**

113 HFM basically represents a spectrum of congenital malformations involving embryological derivatives of the  
114 first and second branchial arches. The multiple anomalies that may coexist in this disorder present considerable  
115 variability in patients with the diagnosis.<sup>26</sup> Males are more frequently affected than females and about 45% of  
116 patients have affected relatives and 5%–10% have affected siblings.<sup>21</sup>

117 The clinical manifestations of HFM comprise a spectrum of disease that is both broad and complex. It is  
118 characterized by a heterogeneous underdevelopment of the facial structures.<sup>27</sup> The fundamental features include  
119 unilateral hypoplasia of the craniofacial skeleton and its overlying malformed soft tissues.<sup>28</sup> Further, the term  
120 hemifacial implies the defect is unilateral, but structures are often affected bilaterally, though to different  
121 degrees, giving the facies an asymmetric appearance.<sup>20</sup> It is a congenital syndrome in which the mandible shows  
122 a spectrum of severity of malformation and the malformation is generally unilateral but may be bilateral, and if  
123 so, is then usually asymmetrical. The findings of study on 89 patients by Loevy HT, Shore SW suggest that the  
124 mandibular deformity associated with HFM does not have an effect on dental maturation compared with the  
125 corresponding non-affected side.<sup>29</sup>

126 The tissues that are more commonly affected in HFM include the condyle and ramus of the mandible,  
127 zygomatic arch, malar bone, external ear, middle ear ossicles, temporal bone, and muscles of facial expression.  
128 HFM may involve some or all of these structures. In fact, HFM is most notable for its vast array of craniofacial  
129 and extra-craniofacial manifestations, including associated malformations of other branchial arch derivatives  
130 such as the eye, vertebrae, and upper heart, as well as malformations of non-arch derivatives also, such as the  
131 kidneys.<sup>30,12,4</sup> The vertebral anomalies most often present are hemivertebrae, block vertebrae,  
132 scoliosis/kyphoscoliosis, and spina bifida mostly in the cervical and thoracic spine and ribs and the prevalence  
133 varies from 8% to 79%.<sup>28</sup> It is a common craniofacial disorder that is known to be etiologically heterogenous  
134 and phenotypic differentiation of the various subgroups remains a challenge. A review of 50 patients with HFM  
135 by Bassila MK et al has yielded data that may help explain different pathogenetic processes. There may be  
136 association of facial nerve palsy, sensorineural hearing loss, or both in a higher percentage of patients than  
137 expected.<sup>31</sup> The incidence of obstructive sleep apnea in population of patients with hemifacial microsomia  
138 approaches 24 percent as discussed in study conducted by Cohen et al. So patients with hemifacial microsomia  
139 should undergo routine screening for obstructive sleep apnea: a positive history warrants polysomnographic and  
140 anatomic workup frequency and severity of airway disorders, especially those leading to upper airway  
141 obstruction and/or obstructive sleep apnea.<sup>32</sup>

#### 142 **DIAGNOSTIC CRITERIA:**

143 Hemifacial microsomia (HFM) is a complex three-dimensional congenital condition that is characterized mainly  
144 by mandibular hypoplasia and unilateral or bilateral microtia; although, other facial structures may be  
145 affected.<sup>33</sup> Familiarity with craniofacial embryology and its associated effects on resultant anatomy leads to a  
146 better understanding of the pathophysiologic basis of such developmental craniofacial disorders which in turn  
147 aids in formulation of precise diagnoses and differential diagnostic considerations.. Additionally, it helps to  
148 establish a search pattern for characteristic radiologic features of many of these anomalies. The first and second  
149 branchial arches are the embryologic origin of many of the structures of the face so a wide variety of congenital  
150 conditions may arise from their contents. The phenotype is highly variable. There may be cardiac, vertebral, and  
151 central nervous system defects, in addition to craniofacial anomalies. Ear deformities predominantly occur  
152 along a spectrum of disorder from the distorted size and shape of the external auricle to anotia.<sup>14</sup>

153 Radiographic evaluation of HFM reveals asymmetric hypoplasia of the maxilla and mandible. One side of the  
154 face may be normally developed or underdeveloped. There are variable degrees of malformation involving the  
155 TMJ, including hypoplasia of the condyle and coronoid. A large variation in the TMJ has been observed on the  
156 more affected side; however, the degree of TMJ disc dysplasia does not appear to correlate with the degree of  
157 mandibular dysplasia.<sup>34</sup> Patients with HFM had more retruded mandibles and maxillae and a more vertical  
158 morphology compared to the reference population. The growth curves showed very high inter-variability among  
159 patients, further strengthening the need for individualized treatment plans that consider all three dimensions and  
160 the severity of the condition.<sup>33</sup> The cranial base axis is not deviated in the patients with HFM compared with the  
161 age-matched controls, and there exists little difference in endocranial morphologic measurements with  
162 increasing severity of HFM. These data are interesting, given the role of the cranial base in facial growth and  
163 the varying hypotheses regarding the mechanism of disease in HFM.<sup>35</sup> Also there are studies which shows that  
164 in persons with hemifacial microsomia certain neuromuscular patterns may differ from the norm because of  
165 missing or underdeveloped muscles and because of the different relationship between the mandible, its attached  
166 muscles, and other structures.<sup>36</sup>

#### 167 **DIFFERENTIAL DIAGNOSIS:**

168 Hemifacial microsomia (HFM) and the branchio-oto-renal syndrome (BOR) are both associated with  
169 malformations of the external ears; preauricular tags, pits, or sinuses; and conductive or mixed hearing loss.  
170 Other overlapping features have been described; including cervical appendages containing cartilage in HFM,

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171 and facial paresis in BOR.<sup>37</sup> Other differential diagnoses include unilateral bony ankylosis, hemifacial  
172 hyperplasia, or lack of oral rehabilitation after traumatic episode.

## 173 MANAGEMENT

174 Oral and maxillofacial malformations, like hemifacial microsomia (HFM) present diagnostic and treatment  
175 challenge to dental professionals and multidisciplinary approach is advised. New therapeutic and clinical  
176 management techniques offer promising interventions that can allow many young patients to have more normal  
177 childhoods. Due to a unilateral deficiency of the mandible and lower face, patients who have HFM have  
178 specific dental needs that require not only restorative and orthodontic but also surgical correction at an early  
179 age.<sup>2</sup> Treatment of patients includes repair of bony asymmetry as well as soft tissue defects and auricular  
180 anomalies. Surgical intervention is individualized based on each patient's deficits.<sup>18</sup> Although surgical  
181 reconstruction is the treatment of choice for auricular deformities that result from hemifacial microsomia, the  
182 implant-retained auricular prosthesis must be considered when surgical reconstruction is not possible.<sup>38</sup>

183 Distraction osteogenesis is an alternative treatment option resulting in new bone formation between  
184 incrementally separated bony segments for patients with facial asymmetry and mandibular hypoplasia.<sup>39,40</sup>  
185 Though, distraction osteogenesis is now a standard procedure for hemifacial microsomia, and various methods  
186 have been described, it is sometimes difficult to obtain the horizontal occlusal plane and facial symmetry.<sup>41</sup>

187 Correction of the skeletal deformity in children with HFM has been advocated to improve growth potential and  
188 reduce secondary deformity. However, contrary reports have suggested that facial asymmetry in hemifacial  
189 microsomia does not increase with growth; therefore, skeletal correction can be postponed, even until  
190 adolescence. Study by Kearns et al demonstrate that hemifacial microsomia is progressive and underscores the  
191 importance of early surgical correction of mandibular asymmetry in this disorder.<sup>42</sup> Even hearing loss,  
192 mastication impairment, breathing problems, speech impediments, and sleep disorders can occur as part of  
193 HFM. Treatments and procedures can occur over many years to improve function and appearance and  
194 undoubtedly can disrupt both child and family. HFM may have long-term effects on psychological development  
195 and social well-being, due to unusual facial appearance, functional problems, and medical treatments.<sup>3</sup>

196 **CONCLUSION:** Hemifacial microsomia is a rare complex craniofacial anomaly causing unilateral facial  
197 hypoplasia with a spectrum of phenotypic differentiation and varied nomenclature. Since there has been little  
198 research on its risk factors and sequelae, several studies, and the subsequent genetic and follow-up studies, are  
199 each groundbreaking in terms of their multi-disciplinary approach and their potential impact on affected  
200 families. As it results in definitive facial asymmetries multidisciplinary approach is appreciable as it can  
201 significantly impact an individual's social and functional well-being.

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