# Hemifacial microsomia: treatment alternatives—a systematic review of literature

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***Objective:*** *To systematically review literature on therapeutic options for treating hemifacial microsomia (HFM), in young patients with growth potential, classifying and comparing the different dentofacial treatment methods.* ***Study design:*** *An independent review of databases (Scopus, Embase, Ovid, Cochrane Library and PubMed) following the Preferred Reporting Items for Systematic reviews and Meta-Analyses (PRISMA), conducted by four evaluators. The protocol of this study was registered in International prospective register of systematic reviews (PROSPERO), under the number CRD42021293076.* ***Results:*** *Between 1970–2021, a total number of 1137 articles were published of which 27 were included in this study according to the selection criteria: one randomized multicentric trial, two case-control studies, three case series and 21 case reports.* ***Conclusions:*** *The most common orthopedic treatments provide vertical stimulation of the maxillary process in the affected side. Orthodontic approaches are mainly applied for vertical correction and stabilization of the occlusal plane. Other treatment options include orthognathic surgery, osteogenic distraction, temporomandibular reconstruction and grafting. It is recommended that prospective clinical randomized controlled studies be conducted using homogeneous pediatric groups with long-term follow-up, to establish recommended evidence-based methods for treating each set of hemifacial microsomia symptoms.*

***Keywords:*** *Hemifacial microsomia, Craniofacial malformation, Facial asymmetry, Orthodontics, Orthopedics, Orthognathic surgery*

## INTRODUCTION

### Background

Hemifacial microsomia (HFM) is a craniofacial syndrome, second in prevalence after cleft/lip and palate, affecting one in 3000–5600 newborn subjects. It is almost always unilateral, as indicated by the name, more prevalent in the right side (70–90% cases), and in male than female adolescents[1–3]. HFM is considered to be a congenital syndrome, that is, genetic but not inherited.

### Description

HFM is a syndrome that causes asymmetrical anomalies in structures derived from the first/second pharyngeal arches: mandible, mandibular condyle, articular cavity, maxillary bone, orbit, auditory canal, ear, soft tissues and muscles innerved by trigeminal and facial nerves[4].

The severity of the disorder is highly variable, depending on the number of structures directly or indirectly involved and the penetrance of the syndrome. The facial asymmetry is due to underdevelopment of one facial side and transversal changes in the mandibular position related to reduced development of temporomandibular joint (TMJ) components and mandibular ramus[4]. Structures adjacent to bony components which

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present vertical changes in the affected side cause maxillary, occlusal and commissural canting. The lack of secondary development of the maxillary, zygomatic and malar bone affects the adjacent soft tissues as well[5].

When facial microsomia is bilateral, the consequent severe mandibular retrognathism affects masticatory, swallowing and respiratory functional processes[6,7]. Depending on the severity of the syndrome, it becomes evident immediately after childbirth and the sequelae are progressive if adequate treatment is not initiated[8].

HFM was first described by Carl F. von Arlt in 1881, but it was also known as Goldenhar syndrome because a variant was described by the ophthalmologist Maurice Goldenhar in 1952, although some authors have not considered both terms to be equivalent until current evidence proved that this was a variant of HFM[9]. It is also known as otomandibular dysostosis, oculo-auriculo-vertebral dysplasia, oral-mandibular syndrome and unilateral hemi-mandibular hypoplasia[10].

## Etiopathogenesis

The etiopathogenesis of HFM is multifactorial and is related to genetic and environmental factors. Family antecedents are reported in just a few cases[9]; however, different mutations and genes are involved in the etiopathogenesis of HFM. Most investigators suggest that the pathogenesis of this syndrome is the altered migration of neural crest cells during embryonal development[11], abnormal vascularization (stapedial artery hemorrhage) during the fourth week of pregnancy[2], and external factors such as the use of vasoactive medication, nicotine and cocaine exposure, thalidomide and hormonal therapy[12]. A higher risk has been reported in mothers with diabetes[13], hypothyroidism, rubeola, celiac disease, multiple pregnancy, vaginal bleeding during pregnancy or premature delivery[9].

## Classifications

Pruzansky classified HFM in three grades: Grade I is characterized by minimal mandibular hypoplasia, with normal structures; Grade II is defined by a small condyle, ramus and sigmoid notch, and variable abnormal shape; Grade III is characterized by the absence of a mandibular ramus, including TMJ[14]. This classification was modified by Kaban *et al.*[15] who divided Grade II into two types: Type IIA and Type IIB. In HFM Grade I, it is fully accepted that all the TMJ components are present and have normal shape, but presenting different grades of hypoplasia. The glenoid cavity has a normal shape and the masticatory muscles are normally developed. In HFM Grade II, the TMJ is functional but the condylar head and glenoid cavity present an abnormal shape. In the Type IIA subcategory, both show hypoplasia and inadequate position allowing a mandibular functional movement, while in Type IIB the mandibular ramus shows hypoplasia and shape and location are abnormal causing TMJ malfunction. In HFM Grade III, the mandibular ramus, condyle and TMJ are absent and the masticatory muscles are not inserted into the mandible[15].

Vento *et al.*[16] established the OMENS (orbit, mandible, ear, nerve, soft-tissue) classification that has been complemented by a series of amendments to evaluate the orbit asymmetry, external ear deformation, nerve compromise and soft tissue deficiencies that might be present in the HFM spectrum of clinical presentations.

## Differential diagnosis

The differential diagnosis of HFM includes pseudo-HFM or hemi-mandibular hypoplasia with condylar coronoid collapse (HHCCC), a condition without any soft tissue defects[17]. With HHCCC, the radiographic image shows collapse of the condyle and the coronoid apophysis, a condition that was not included in the classifications of Pruzansky and Kaban[14,15]. It usually shows ramus, condyle and glenoid cavity hypoplasia[17]. In both entities, chin deviation toward the hypoplastic side is common. The temporal fossa (glenoid cavity) is always present in HHCCC, but not in HFM[2].

It is also important for a differential diagnosis to include a genetic analysis to rule out other syndromes such as Treacher-Collins, Miller-Dierker, Parry Romberg, CHARGE, Townes-Brocks, Branquio-oto renal, among other facial alterations[4]. The HFM diagnosis is sufficiently based on a detailed physical examination, clinical records and the analysis of 2D and 3D craniofacial images, but it should be complemented by molecular analysis interpreted by a geneticist to understand its characteristics and any familiar components[18].

## Treatment

Regarding the treatment options, the literature reports different modalities depending on factors such as the patient's age, severity of symptoms and the specialist who initiates the treatment[10,22,23].

The clinical presentation of HFM includes dental and occlusal findings that require collaboration between orthodontists, dentofacial orthopedists, and maxillofacial surgeons.

Multidisciplinary team management is recommended due to the potential for ocular, auditive, neurologic, cervical, gastro-intestinal, kidney and cardiac compromise[19–21]. The skeleto-dento-facial treatment objectives are:

—To increase the mandibular size and soft tissues associated with the affected side

—To provide a functional simulation of the TMJ when this structure is absent

—To correct secondary deformities in the maxilla

—To improve dental position and smile arch

—To correct dental canting

—To establish a functional occlusion

—To increase the range of buccal opening when it is limited

—To improve facial and dental esthetics

The treatment of HFM includes surgical procedures such as osteogenic distraction[24] and orthognathic surgery to correct the asymmetric growth of bone structures[25,26]. Orthopedic interventions use multiple functional appliances, mainly the asymmetrical (AFA)[27] or hybrids[28], which use unilateral bite blocks to favor the vertical development of the affected side and also asymmetrical maxillary expansion[24]. As for orthodontic treatments, it is common to use intermaxillary elastics and temporary anchorage devices (TADs)[29,30] to establish differential forces.

The combined treatments are variable according to the affected structures, the severity of impairments, the age of the patient, and the expertise and preferences of the clinical team. Currently, there are no established protocols for treating HFM.

## Relevance of the present systematic review of literature

HFM is a complex deformity disorder that poses a challenge to clinicians. The treatment is almost always institutional and intra-hospital and must be initiated from childbirth, so it is not commonly seen in the independent professional practice. Mild cases can be misdiagnosed from isolated symptoms, which highlights the importance of knowing about the condition, its variability and the treatment alternatives. A systematic review of this topic provides a complete and comprehensive view of the treatment approaches, including orthodontics, orthopedic and surgical common options to manage HFM and the related sequelae.

## METHOD

This systematic review of literature was carried out according to the recommendations suggested by the PRISMA statement[31].

## Eligibility of articles

Study designs: Randomized controlled clinical trials, observational retrospective and prospective studies, case series, case-control and case reports.

Participants: The patients included in the study had an HFM diagnosis and were young enough to still have a potential for growth and development including residual growth (less than 22 years). There was no distinction for gender, ethnicity nor racial identity.

Interventions: The studies must describe orthodontic/orthopedic treatments with or without surgical procedures to correct HM and be free of treatment-related sequelae.

Outcome measurements: Type of treatment provided efficacy of the therapy in meeting the treatment objectives (maxillary canting correction, asymmetry correction, malocclusion and mandibular growth correction in the affected side).

## Search methods

Sources of information: The data bases consulted were Scopus, Embase, Ovid, Cochrane Library and PubMed.

Electronic search: The time Interval was 1970—November 2021. No language or date of publication restrictions was applicable. The search equation used was:

((((((((((((((((((((Goldenhar (Title/Abstract)) OR (Oculoauriculovertebral Dysplasia (Title/Abstract))) OR (Dysplasia, Oculoauriculovertebral (Title/Abstract))) OR (Oculoauriculovertebral Dysplasias (Title/Abstract))) OR (Oculoauriculovertebral Spectrum (Title/Abstract))) OR (Oculoauriculovertebral Syndrome (Title/Abstract))) OR (Craniofacial Microsomia (Title/Abstract))) OR (Microsomia, Craniofacial (Title/Abstract))) OR (Facioauriculovertebral Dysplasia (Title/Abstract))) OR (Dysplasia, Facioauriculovertebral (Title/Abstract))) OR (Goldenhar Gorlin Syndrome (Title/Abstract))) OR (Goldenhar Disease (Title/Abstract))) OR (Lateral Facial Dysplasia (Title/Abstract))) OR (Oral Mandibular Auricular Syndrome (Title/Abstract))) OR (Otomandibular Dysostosis (Title/Abstract)))) OR (First and Second Branchial Arch Syndrome (Title/Abstract))) OR (Facioauriculovertebral Sequence (Title/Abstract))) OR (Hemifacial Microsomia (Title/Abstract))) OR (Craniofacial Microsomias (Title/Abstract))) AND ((((orthognathic (Title/Abstract)) OR (orthopedic (Title/Abstract))) OR (orthodontic (Title/Abstract))) OR (dentistry (Title/Abstract)))

## Data extraction and analysis

Selection of articles: The first selection was performed by reading abstracts and/or summaries. Data extraction and risk of bias were performed independently by two investigators (DA, DR). In the event of a disagreement, a consensus for selection of the article was obtained. Both investigators filled a table for extraction and analysis of the variables to be considered.

The data list included:

Type of treatment
- ◯ Orthodontics
- ◯ Maxillary Orthopedics
- ◯ Orthognathic, maxillofacial surgery

Variables in the treatment used
- ◯ Fixed appliances such as brackets
- ◯ Intermaxillary elastics
- ◯ Temporary anchorage devices (TADs)
- ◯ Auxiliary treatment (including maxillary expansion)
- ◯ Functional Orthopedics
- ◯ Extraoral Orthopedics
- ◯ Orthognathic maxillofacial surgery
- ◯ Osteogenic distraction surgery
- ◯ Complementary therapies

Outcome variables
- ◯ Correction of occlusal plane canting
- ◯ Correction of malocclusion
- ◯ Condylar and mandibular growth of the affected side
- ◯ Asymmetry Correction
- ◯ Treatment time
- ◯ Follow up time

Population characteristics included in the study
- ◯ Age
- ◯ HM Classification
- ◯ Affected side
- ◯ Number of patients of each gender

Risk of bias evaluation

(1) For case reports and case series: the instrument used by Murad *et al.*[32]

(2) For observational cohort and case-control: New Castle Ottawa

(3) For randomized controlled studies: Cochrane ReMan

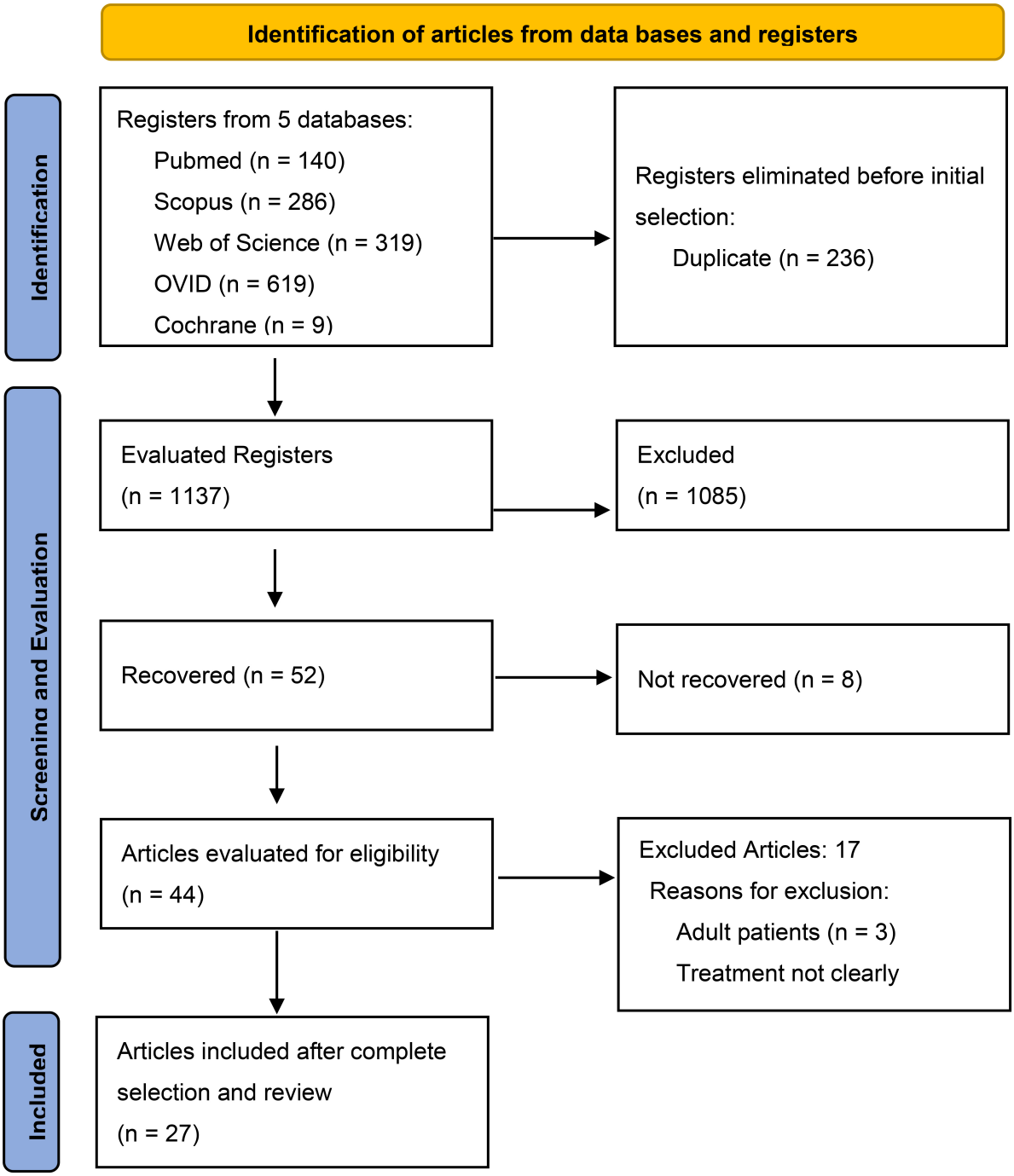


**Figure 1: Flow Diagram of article selection according to the PRISMA statement.**

**Table 1: Description of articles selected for systematic review and types of treatment used.**

| First Author | Year | Country | Journal | Design | N | Age (years) | Hemifacial microsomia (HFM) Classification | Side | Fixed Appli-ance (Yes/No) | Maxillary Orthope-dics (Yes/No) | Maxillofacial orthog-nathic surgery (Yes/No) |
|---|---|---|---|---|---|---|---|---|---|---|---|
| S. Perrotta[17] | 2020 | Italy | J Craniofac Surg | Case Report | 2 | 6–7 | No indication | Left | No | Yes | No |
| Ayami Ito[33] | 2020 | Japan | J Contemp Dent Pract | Case Report | 1 | 8 | IIB Prusansky | Right | Yes | Yes | No |
| E. William Amm[29] | 2012 | Lebanon | Am J Orthod Dentofac Orthop | Case Report | 1 | 17 | No indication | Left | Yes | No | Yes |
| T Yamashiro[34] | 1997 | Japan | Angle Orthod | Case Report | 1 | 10 | No indication | Left | Yes | Yes | Yes |
| Robinson M.[35] | 1970 | USA | Am J Orthod Dentofac Orthop. | Case Report | 1 | 7 | No indication | Left | Yes | Yes | Yes |
| S-H. Choi[24] | 2014 | Korea | Am J Orthod Dentofac Orthop | Case Report | 1 | 22 | I Prusansky | Left | Yes | Yes | Yes |
| G. Zanardi[25] | 2012 | Brazil | Am J Orthod Dentofac Orthop | Case Report | 1 | 12 | IIB | Left | Yes | No | Yes |
| D. Cassi[8] | 2017 | Italy | Case Rep Dent | Reporte de caso | 1 | 2 | IIA Prusansky | Left | No | Yes | No |
| S. Kim[26] | 2012 | Korea | J Craniofac Surg | Case Report | 1 | 4 years 10 months/12 years 3 months | IIB Prusansky | Left | Yes | No | Yes |
| C. Moulin-Romse[27] | 2004 | Belgium | J Orthod | Case Report | 1 | 10.5 | No indication | Right | Yes | Yes | Yes |
| P. Agurto Veas[36] | 2018 | Chile | J Craniofac Surg | Case Report | 3 | 11, 10, 10 | 1-I2-IIA<br>2-3-IIB Prusansky | 1-left<br>2-left<br>3-right | Yes | No | Yes |
| Mahtab Nouri[37] | 2014 | Iran | Irán Red Crescent Med J | Case Report | 1 | 7 | Mild | Left | Yes | Yes | No |
| T. El-Bialy[45] | 2010 | Canada | J Clin Trials | Case Series | 5 | 3–11(3, 4, 7, 11, 11) | Class II, Class I, Class II, Class I, Class II | No report | No | Yes | No |


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**Table 1: Continued.**

| First Author | Year | Country | Journal | Design | N | Age (years) | Hemifacial microsomia (HFM) Classification | Side | Fixed Appli-ance (Yes/No) | Maxillary Orthope-dics (Yes/No) | Maxillofacial orthog-nathic surgery (Yes/No) |
|---|---|---|---|---|---|---|---|---|---|---|---|
| Silvestri, A[46] | 1996 | Italy | J oral Maxillofac Surg | Case Series | 16 | 5–12 | No indication | 6 left, 10 right | Yes | Yes | No |
| Sarnäs, K.-V.[38] | 1982 | Sweden | Am J Orthod Dentofac Orthop | Case Report | 1 | 8 | No indication | Right | No | Yes | No |
| Seo, J-S.[39] | 2015 | Korea | Maxillofac Plast reconstr Surg | Case Report | 1 | 9 | IIA Prusansky | Left | Yes | No | Yes |
| Chung, N. H.[40] | 2020 | Korea | Korean J Orthod | Case Report | 1 | 8 | IIA Prusansky | Right | Yes | Yes | Yes |
| Wang, J.[48] | 2019 | China | Am J Orthod Dentofac Orthop | Observational retrospective | 10 | 7 Average | No indication | No report | Yes | Yes | No |
| Takashima, M.[28] | 2003 | Japan | Cleft Palate Craniofac J | Case Report | 1 | 8 | No indication | Left | No | Yes | Yes |
| Mejia-Gomez C M.[41] | 2013 | Colombia | J Clin Pediatr Dent | Case Report | 1 | 6 | No indication | Left | No | Yes | No |
| M. J. Papagrigorakis[30] | 2012 | Greece | Angle Orthod | Case Report | 1 | 11 | Bilateral skeletal deformationl Kaban IIb | Bilateral | Yes | No | Yes |
| Azita Tehranchi[47] | 2001 | Iran | Am J Orthod Dentofac Orthop | Case Series | 10 | 2–7 | No indication | 5 left/5 right | Yes | Yes | Yes |
| C. Suppapinyaroj[49] | 2020 | China | J Oral Maxillofac Surg | Observational retrospective | 20 | 20.72 ± 2.96 | 19 Pruzansky-Kaban IIB; 1 IIA. | 13-right; 7-left | Yes | No | yes |
| Xiaohui Qiu[50] | 2020 | China | J Craniomaxillofac Surg | RCT multicentric | 70 | 7.629 ± 3.172 | II Prusansky | No indication | Yes | Yes | Yes |
| R. Leonardi[42] | 2007 | Italy | J Craniomaxillofac Surg | Case Report | 1 | 6.5 | II A–M2B | Right | No | Yes | No |
| Balaguhan Balasubra-manian[43] | 2021 | India | World J Dent | Case Report | 1 | 20 | IIA | Right | Yes | No | Yes |
| H. Yamada[44] | 2020 | Japan | J Am Dent Assoc | Case Report | 1 | 10 | IIB | Left | Yes | Yes | No |



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**Table 2: Treatment Characteristics.**

| # | First Author | Fixed Appliance (bracket-type) | Intermaxillary elastics | Temporary anchor device (TAD) | Auxiliary treatment (including maxillary expansion) | Functional Orthopedics | Extraoral orthope-dics | Maxillofacial orthognathic surgery | Osteogenic distrac-tion (OD) surgery | Complementary therapies |
|---|---|---|---|---|---|---|---|---|---|---|
| 1 | S. Perrotta[17] | | | | Vertical Expansion | Asymmetric functional appliance (AFA) | | | | |
| 2 | A. Ito[33] | Standard 0.18 | | TAD in first molar zone | Mandibular expansion | | | | | |
| 3 | E-W. Amm[29] | Standard 0.22 | Class III | TAD mandibular | | | | Mandibular Osteotomy | OD | |
| 4 | T. Yamashiro[34] | Standard 0.22 | | | Quad Helix maxillary expansion | Frankel and AFA | | Orthognathic mandibular advance and genioplasty | | |
| 5 | M. Robinson[35] | Standard | | | | | Cervical asym-metric traction | Condylar Elevation | | |
| 6 | S-H. Choi[24] | Standard | Vertical elastics | 4 palatal TAD | Hyrax palatal expansion | | | Mandibular Osteotomy | OD | |
| 7 | G. Zanardi[25] | Roth 0.22 | Class II Elastics and box | | | | | Maxillary impactation, mandibular advance and genioplastia | | |
| 8 | D. Cassi[8] | | | | | AFA | | | | |
| 9 | S. Kim[26] | Standard | Intermaxillary and trans arch elastics | TADs in premolar mandibular zone healthy side | | | | Maxillary asymmetric impactation-unilateral mandibular osteotomy | Mandibular OD | |
| 10 | C. Moulin-Romsée[27] | Standard | | | | AFA | | Bone graft in mandibular angle | | |
| 11 | P. Agurto Veas[36] | 1 no, 2 standard 3 standard | | | | | | Orthognathic mandibular surgery | 1- no, 2-OD 3-OD | |


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**Table 2: Continued.**

| # | First Author | Fixed Appliance (bracket-type) | Intermaxillary elastics | Temporary anchor device (TAD) | Auxiliary treatment (including maxillary expansion) | Functional Orthopedics | Extraoral orthope-dics | Maxillofacial orthognathic surgery | Osteogenic distrac-tion (OD) surgery | Complementary therapies |
|---|---|---|---|---|---|---|---|---|---|---|
| 12 | M. Nouri [37] | Roth 0.22 | Class II Elastics (affected side) and Class III (contralateral) | | | AFA y and bite-blocks | Head Gear | | | |
| 13 | T. El-Bialy [45] | | | | | AFA | | | | LIPUS (low fre-quency pulse ultra-sound) |
| 14 | A. Silvestri [46] | Standard | | | | Bionator and AFA | | | | |
| 15 | K-V. Sarnäs [38] | | | | | Herbst | | | | |
| 16 | J. Seo [39] | Standard | | | | | | Genioplasty and mandibular body increase | OD | |
| 17 | N-H. Chung [40] | Preadjusted Brackets Roth 0,022 | Vertical Elastics | | | posterior unilateral bite block | | Mandibular osteotomy | OD | |
| 18 | J. Wang [48] | | Elastics 3,5 ounces and 1/4 inch | TAD in superior and inferior alveolus (healthy side) | | Asymmetric bite plate and functional appliance | | Mandibular Osteotomy | OD | |
| 19 | M. Takashima [28] | | | | | Hybrid functional appliance | | Mandibular Osteotomy | OD in left side mandible | |
| 20 | C-M. Mejia-Gomez [41] | | | | | KLAMT Modified regulator | | | | |
| 21 | M-J. Papagrigorakis [30] | Fixed appliance | | TAD (palatal) | Fast maxillary expansion | | | Mandibular Osteotomy | OD vertical elonga-tion | |



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**Table 2: Continued.**

| # | First Author | Fixed Appliance (bracket-type) | Intermaxillary elastics | Temporary anchor device (TAD) | Auxiliary treatment (including maxillary expansion) | Functional Orthopedics | Extraoral orthope-dics | Maxillofacial orthognathic surgery | Osteogenic distrac-tion (OD) surgery | Complementary therapies |
|---|---|---|---|---|---|---|---|---|---|---|
| 22 | A. Tehranchi[47] | Edgewise brackets (0.018 inch) | | | | Hybrid functional appliance | | Mandibular Osteotomy | DO (ramus os-teotomy) | |
| 23 | C. Suppapinyaroj[49] | Preadjusted | Short class II or oblique long elastics | | | | | Maxillary asymmetric Impactation, mandibular osteotomy and genioplasty | OD | |
| 24 | X. Qiu[50] | MBT tubes in permanent first mo-lars/deciduous second molars in affected upper side and inferior contralateral | Intermaxillary elastics 1/4, 3.5 Oz | | | Occlusal ferule gradual shortage in affected side | | Mandibular osteotomy | OD vertical ramus traction | |
| 25 | R. Leonardi[42] | | | | | Andressen modified and AFA | | | | |
| 26 | B. Balasubrama-nian[43] | MBT fixed appliance | Intermaxillary Elastics | | Resin | | | Lefort I asymmetric, osteotomy, sagittal bilateral mandibular and genioplasty | | |
| 27 | H. Yamada[44] | Standard | Intermaxillary elastics | | Bite blocks | Maxillary lingual Arch with accessory springs | | | | |



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**Table 3: Treatment time, outcomes and long-term follow up.**

| First author | Treatment time (years) | Follow up time (years) | Occlusal plane cant Correction (Yes, No, No report) | Malocclusion correction (Yes, No, No report) | Mandibular growth in affected side (Yes, No, No report) | Asymmetry Correction (Yes, No, No report) |
|---|---|---|---|---|---|---|
| S. Perrotta[17] | No report | 3 | Yes | No report | Yes | Yes |
| A. Ito[33] | 7 | 1.5 | No | Yes | No | No |
| E-W. Amm[29] | 3 | 3 | Yes | Yes | Yes | Yes |
| T. Yamashiro[34] | 2 | 3 | No | Yes | No | No report |
| M. Robinson[35] | 2.2 | 2 | Yes | Yes | No | No report |
| S-H. Choi[24] | 2.2 | 1 | Yes | Yes | Yes | Yes |
| G. Zanardi[25] | 1 | 3 | No | Yes | No | Yes |
| D. Cassi[8] | 3 | 0.7 | Yes | Yes | Yes | Yes |
| S. Kim[26] | 3 | 0.6 | Yes | Yes | Yes | Yes |
| C. Moulin-Romsée[27] | 3 | 3 | Yes | Yes | Yes | Yes |
| P. Agurto Veas[36] | 4 | 3 | Yes | Yes | Yes | Yes |
| M. Nouri[37] | 6 | No report | Yes | Yes | Yes | Yes |
| T. El-Bialy[45] | 0.9 | No report | No | No | Yes | No |
| A. Silvestri[46] | No report | No report | No | No | Yes | No |
| K-V. Sarnäs[38] | 0.6 | No report | No | Yes | Yes | No |
| J. Seo[39] | 10 | No report | report | Yes | Yes | Yes |
| N-H. Chung[40] | 2 | 10 | No report | Yes | No | No |
| J. Wang[48] | 0.6 | No report | Yes | Yes | Yes | Yes |
| M. Takashima[28] | 1.3 | 1 | Yes | No | Yes | Yes |
| C-M. Mejia-Gomez[41] | 3 | No report | No report | Yes | Yes | Yes |
| M-J. Papagrigorakis[30] | 2.2 | 1 | No report | Yes | No report | No report |
| A. Tehranchi[47] | No report | 2.1 | Yes | No report | No report | No report |
| C. Suppapinyaroj[49] | 2.5 | No report | No report | No report | Yes | Yes |
| X. Qiu[50] | No report | 2.5 | Yes | Yes | Yes | Yes |
| R. Leonardi[42] | 4 | 2 | No report | Yes | Yes | Yes |
| B. Balasubramanian[43] | 1.5 | 3 | Yes | Yes | No report | No report |
| H. Yamada[44] | 4.6 | 5.1 | Yes | Yes | Yes | Yes |



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**Table 4: Risk of bias. Results of the assessment.**

| First Author | Selection | Proof | | Causality | | | Report Presentation | Total |
|---|---|---|---|---|---|---|---|---|
| | CASE REPORTS AND CASE SERIES | | | | | | | |
| | Patient selection according to therapeutic needs? | Treatment explained in detail? | Adequate determination of the outcome? Is it measurable? | Adequate diagnosis established? | Adverse effects of the treatment are presented? | Total duration of treatment is presented? The results are consistent and can be extrapolated? | Follow-up time sufficiently long? | Cases described with sufficient detail? | |
| S. Perrotta [17] | 5 | 5 | 4 | 5 | 3 | 4 | 5 | 4 | 35 |
| A. Ito [33] | 6 | 6 | 6 | 5 | 4 | 5 | 5 | 5 | 42 |
| E-W. Amm [29] | 5 | 5 | 6 | 5 | 4 | 5 | 6 | 5 | 41 |
| T. Yamashiro [34] | 4 | 4 | 4 | 4 | 3 | 5 | 3 | 4 | 31 |
| M. Robinson [35] | 5 | 5 | 4 | 5 | 3 | 5 | 4 | 4 | 35 |
| S-H. Choi [24] | 5 | 5 | 5 | 4 | 4 | 5 | 5 | 5 | 38 |
| G. Zanardi [25] | 5 | 4 | 5 | 4 | 4 | 4 | 5 | 5 | 36 |
| D. Cassi [8] | 6 | 5 | 3 | 3 | 3 | 5 | 3 | 5 | 33 |
| S. Kim [26] | 5 | 5 | 5 | 3 | 3 | 4 | 3 | 5 | 33 |
| C. Moulin-Romsée [27] | 4 | 4 | 4 | 5 | 5 | 5 | 5 | 4 | 36 |
| P. Agurto Veas [36] | 4 | 3 | 3 | 4 | 2 | 3 | 3 | 3 | 25 |
| M. Nouri [37] | 5 | 4 | 4 | 4 | 3 | 4 | 3 | 4 | 31 |
| T. El-Bialy [45] | 4 | 4 | 5 | 5 | 4 | 6 | 4 | 5 | 37 |
| A. Silvestri [46] | 5 | 6 | 5 | 6 | 4 | 5 | 5 | 4 | 40 |
| K-W. Sarnäs [38] | 3 | 5 | 3 | 3 | 3 | 5 | 4 | 4 | 30 |
| J. Seo [39] | 6 | 6 | 5 | 5 | 4 | 6 | 5 | 5 | 42 |
| N-H. Chung [40] | 6 | 6 | 5 | 6 | 4 | 5 | 5 | 5 | 42 |
| J. Wang [48] | 5 | 5 | 6 | 5 | 4 | 5 | 3 | 5 | 42 |
| M. Takashima [28] | 5 | 5 | 6 | 4 | 4 | 5 | 3 | 5 | 37 |
| C-M. Mejia-Gomez [41] | 5 | 4 | 3 | 5 | 4 | 5 | 3 | 4 | 33 |
| M-J. Papagrig-orakis [30] | 5 | 5 | 5 | 3 | 4 | 5 | 3 | 5 | 35 |
| A. Tehranchi [47] | 5 | 6 | 5 | 3 | 4 | 5 | 3 | 5 | 36 |
| C. Suppapin-yaroj [49] | 5 | 5 | 5 | 5 | 3 | 5 | 3 | 5 | 36 |
| X. Qiu [50] | 5 | 5 | 5 | 5 | 4 | 5 | 5 | 5 | 36 |


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**Table 4: Continued.**

| CASE REPORTS AND CASE SERIES | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|
| First Author | Selection | Proof | | Causality | | | | Report Presentation | |
| | Patient selection according to therapeutic needs? | Treatment explained in detail? | Adequate determination of the outcome? Is it measurable? | Adequate diagnosis established? | Adverse effects of the treatment are presented? | Total duration of treatment is presented? The results are consistent and can be extrapolated? | Follow-up time sufficiently long? | Cases described with sufficient detail? | Total |
| R. Leonardi[42] | 5 | 6 | 5 | 4 | 5 | 5 | 5 | 6 | 41 |
| B. Balasubramanian[43] | 6 | 5 | 5 | 5 | 5 | 5 | 6 | 5 | 42 |
| H. Yamada[44] | 5 | 5 | 5 | 5 | 5 | 5 | 6 | 5 | 41 |
| Average | 5 | 5 | 4.6 | 4.4 | 3.8 | 4.8 | 4.3 | 4.6 | 36.5 |

| CASE CONTROL STUDIES | | | | |
|---|---|---|---|---|
| First Author | Selection (/4) | Comparability (/2) | Outcome/ Exposition (/3) | Result |
| Wang, J. | ⋆⋆⋆ | ⋆⋆ | ⋆⋆ | 7 |
| C. Suppapinyaroj | ⋆⋆⋆ | ⋆⋆ | ⋆⋆ | 7 |

*Interpretation: Individual scores for case reports and case series: Low (1–2), moderate (3–4), high (5–6). Total scores for case reports and case series: low (8–16) moderate (17–32), high (33–48).*
*Case control scores: selection maximum (⋆⋆⋆), comparability maximum (⋆⋆) result maximum (⋆⋆⋆).*



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## RESULTS

The electronic search detected 1137 registers published between 1970–2021. After the selection process, 44 articles were evaluated and 27 met inclusion criteria: 21 case reports[8,17,24–30,33–44], three case series[45–47], two case-control studies[48,49], and one randomized controlled clinical trial (RCCT)[50] (Fig. 1).

There were 25 excluded or not recovered registers (Supplementary Table 1).

A summary of patient characteristics in the studies shows that the age at initial treatment ranged from 2–22 years and the patient distribution by gender was 35 males (41%) and 50 females (59 %) (Table 1). Regarding the affected side in the reported cases, it was on the left side in 34 patients; on the right side in 35 patients and one was bilateral (not hemifacial). Additionally, Table 1 indicates the article authors, year of publication, country of study, journal, and HM classification of the cases.

Regarding the type of treatment, 19 studies described the use of orthodontics, 19 the use of maxillary orthopedics, and 16 the use of maxillofacial surgery. Twelve studies used orthodontics + orthopedics; 15 orthodontics + surgery; 8 orthopedics + surgery; and eight orthodontics + orthopedics + surgery (Table 1).

The orthodontic treatments described in 18 studies included the use of brackets: 11 used intermaxillary elastics (Class III, Class II, asymmetric, vertical and trans-arch), six used TADs, and five used maxillary expansion with Quad Helix. The 16 studies that featured orthopedic functional treatment used Frankel or Bionator functional appliances while two studies used extraoral orthopedics. The surgical treatments included maxillary surgery in four studies, mandibular surgery in 16 studies, genioplasty in five studies, and osteogenic distraction in 11 studies (Table 2).

The outcome variables were defined as significant total or partial correction of an anomaly as reported by the authors. Successful correction of occlusal plane canting was reported in 15 cases, correction of a malocclusion in 21 cases, stimulation of mandibular and condylar growth on the affected side in 19 cases, and correction of an asymmetry in 17 cases. Treatment time ranged from 5 months to 12 years (average: 3 years) and the follow up period averaged 2.6 years with a maximum of 10 years in one study[49] (Table 3).

### Risk of bias assessment

The Murad *et al.*[32] scale for analyzing bias in case reports and case series was modified by assigning a numerical value to Questions 1–6, classifying high risk bias as 1–2, moderate risk as 3–4, and low risk as 5–6. Four investigators (D.L, D.R, D.A and C.M: two of them are experts in systematic reviews) performed the risk of bias analysis and checked previous verification of the inter-observer agreement in the evaluations (Table 4).

In the case report and case series studies, four articles presented moderate risk of bias while the other one presented a low risk of bias relative to the description of adverse effects, differential diagnosis and long-term follow up (Table 4).

The two case-control studies evaluated for risk of bias using the Newcastle Ottawa instrument that evaluates selection criteria, comparability, and exposure presented low risk of bias (Table 4).

The RCCT study that was analyzed with the Cochrane instrument (Program Review Manager 5.4.1) qualified as having a low risk of bias in all aspects (Supplementary Fig. 1).

## DISCUSSION

The present systematic review of literature, which focused on orthopedic/orthodontic treatments, indicates that HFM in children and adolescent patients is treated by various different methods, according to the variability and severity of the symptoms. Orthopedic and orthodontic techniques were used independent of the patient's age and followed clinical preferences. The treatments included surgery and other interventions according to the tissue and structure affected and the evolution of the disorder.

It was remarkable to find that only one multicentric randomized clinical trial has been published. This study by Qiu *et al.*[50] included 70 patients and was the only publication found with a high level of evidence. Then, two observational studies (Wang *et al.*[48] 2019 and Suppapinyaroj *et al.*[49] 2020) included 10 and 20 patients, respectively. The rest of the studies were case reports or series of cases and were very heterogeneous. Therefore, it was impossible to perform a meta-analysis or to provide guidelines based on solid scientific evidence.

Regarding HFM treatment, 19 articles described orthopedic cases[8,17,24,27,28,33–35,37,38,40–42,44–48,50] involving patients who were aged 2–12 years at the beginning of treatment while one applied mini-screw assisted maxillary expansion in a 22 years old patient[24].

In 10 articles[8,17,27,28,34,37,45–48], asymmetric activators of variable design were used, aiming to stimulate maxillary vertical growth in the affected side and to control or block growth in the contralateral side, correcting a maxillary cant and concomitant occlusion. The reported outcome obtained with these mechanics was satisfactory in all the articles. In reference to this technique, Meazzini *et al.*[51] postulated that in less severe cases where a final surgery was not necessary, this approach provided a symmetric smile and acceptable maxillary position. In combined treatment cases, including osteogenic distraction, the orthopedic treatment helped to correct the occlusal plane, although the effect was more dental-alveolar than skeletal.

Another orthopedic technique for treating HFM is the expansion or maxillary disjunction[17,24,30,33,34] with Quad Helix or Hyrax. In some of these cases, mini-screws are used (MARPE). Kuaw *et al.*[52], making reference to this technique, explained that maxillary expansion in patients with asymmetry and posterior cross-bite improves the functional position of the mandible by stimulation of neuromuscular balance that provides acceptable masticatory pattern and occlusal stability.

The age at which the treatment is initiated is a very important variable when the objective is to stimulate craniofacial growth with orthopedic appliances. Many authors, including Bjork[53], Nakai *et al.*[54], and Aarts *et al.*[55] consider that there is a potential for residual growth in the TMJ and craniofacial

structures of patients up to 22 years of age. This is why we included a 22 years old in the study[24].

Sidiropoulou *et al.*[56] emphasized that the treatment of patients with congenital abnormal condyles and facial asymmetry should be treated as early as possible to stimulate the normal growth of deficient tissues and induce bone apposition, thus hopefully avoiding the need for future surgical interventions. Melsen *et al.*[57], remarked that two benefits of early treatment with functional appliances are (1) There are better results with surgery when it is necessary anyway, (2) Surgical reconstruction is almost totally devoted to improving the hard tissue deficiencies. In HM cases, the problem is not only the lack of skeletal elements but also of muscle and other soft tissues that, while stimulated by a functional appliance, will provide a better environment for the surgical procedure.

Orthodontic treatments were included as an integral treatment in 20 articles[24–27,29,30,33–37,39,40,43,44,46–50], but never as the only solution because it is a dentoalveolar approach that has just a small impact on the skeletal component. Eleven of the articles[24,26,27,29,33–36,39,44,46] described the use of standard appliances and eight pre-adjusted systems[25,30,37,40,43,47,49,50], mostly vertical and sagittal elastics to stimulate alveolar growth to correct an occlusal cant, sagittal discrepancies and provide occlusal adjustment. In six articles[24,26,29,30,33,48], the use of elastics was combined with temporal anchorage devices (TADs) to establish skeletal anchorage additional to the dentoalveolar support. In general, the orthodontic treatment focused on the occlusal stability obtained by an adequate cusp-fossa relationship to obtain the best mandibular position and assist in improving the symmetry and muscle balance to improve occlusal function.

Surgical interventions are corrective and include the dynamics of HFM as the main approach or in addition to orthopedic/orthodontic treatments. Osteogenic distraction (OD) is used to stimulate mandibular growth in the affected side and orthognathic surgery is used to correct the size and position of the compromised structures. Additionally, the use of grafts or articular prosthesis and plastic and reconstructive surgery is added as necessary. In 16 of the articles included in the review, mandibular surgery was the common surgical intervention[24–30,34–36,39,40,43,47,49,50], and eleven articles[24,26,28–30,36,39,40,47,49,50] included OD, always accompanied by orthognathic mandibular surgery and maxillary surgery[26,49] or mentoplasty[39,49]. Three articles described triple surgery involving the maxilla, mandible and menton[25,43,49]. Only in the Balasubramanian *et al.*[43] report was this accompanied by OD.

The surgical reports in general indicated that surgery was used for the esthetic, anatomic and functional aspects of HM treatment, and concluded that the treatment was not able to completely correct facial asymmetry, but in order to improve personal and social well-being, they should be applied during the period of facial growth, even though the prognosis might be poor and additional surgical procedures might be needed later[25].

Complementary therapies indicated are physiotherapy to recover or improve postural alterations, mastication, respiration[58]; and low intensity ultrasound to stimulate the growth of hard and soft tissues. El-Bialy *et al.*[45] have suggested the use of ultrasound to stimulate mandibular growth in the affected side, but without a conclusive description of the outcome.

## CONCLUSIONS

This systematic literature review demonstrated that:

1. HFM requires a multidisciplinary management and includes the use of orthopedic functional asymmetric appliances for vertical stimulation of the alveolar process, and in some cases expanders to produce maxillary expansion. Orthodontic appliances are additionally required to provide occlusal stability and vertical correction (occlusal cant) in addition to intermaxillary elastics with dental-alveolar support or skeletal support with TADs.
2. The evidence derived from the current literature is of poor quality; therefore, well-designed prospective clinical trials are necessary with homogeneous samples and long-term follow up.
3. It is not yet possible to establish guidelines for treating each set of symptoms in the HFM syndrome due to the current lack of sufficient scientific evidence.

## CONFLICT OF INTEREST

The authors state that they had no conflict of interest during the conduct of the study and no source of funding or interest was obtained.

## SUPPLEMENTARY MATERIAL

Supplementary material associated with this article can be found, in the online version, at https://oss.jocpd.com/files/article/1582321246260871168/attachment/Supplementary%20Materials.docx.

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