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Structural comparison of hemifacial microsomia mandible in different age groups by three-dimensional skeletal unit analysis

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ABSTRACT

Purpose: The goal of this study was to understand the three-dimensional (3D) structural characteristics of hemifacial microsomia (HFM) mandible in terms of skeletal units, especially to locate the underdeveloped skeletal regions for treatment. Another goal was to compare the HFM structure of different age groups to understand growth potential relevant to treatment scheduling.
Materials and methods: We reconstructed 3D mandibles from computed tomographic images of French and Korean patients with HFM (N = 28; group II) and normal subjects (N = 27; group I). Each mandible was classified by Pruzansky's HFM types I, II and III, and by age group (child, adolescent, and adult). The mandible was divided into skeletal units, and geometrical representation by skeletal unit line was performed, including the condylar, body, coronoid, and angular units. Their length and angulations were measured and statistically analyzed.
Results: The results showed that the affected condylar unit in type II HFM and the condylar/coronoid unit in type III were smaller in young age groups than were other units. The angulation between the skeletal units in type II, though not type III, tended toward normalcy with age, but not to the normal degree of angulations in group I.
Conclusion: Our study shows the major involvement of condylar unit and minor involvement of body unit for HFM, improving with age in type II. The mandibular skeletal unit analysis seems to be a useful tool for individualized diagnosis, allowing identification of the major etiopathogenic area and treatment planning, including a simulation to set up a regimen for successful reconstruction of HFM.

1. Introduction

Hemifacial microsomia (HFM) is the second most frequent congenital dysmorphosis in the craniofacial region (Figueroa and Pruzansky, 1982). It presents a broad spectrum of asymmetries in various facial regions including craniofacial skeleton, ear, muscles, and connective tissues (Gougoutas et al., 2007; Ahiko et al., 2015; Neiva et al., 2015). Mandibular dysmorphosis being the main phenotypic manifestation of HFM, this region has attracted considerable attention, resulting in many focused studies. The dysmorphic mandible of HFM shows variable phenotype, ranging from minimal underdevelopment of the condyle to the absence of the ascending ramus and the condyle (Grabb, 1965; Grayson et al., 1983; Ahiko et al., 2015).

There have been different ways of evaluating the mandibular structures, such as anthropometric or cephalometric measurements (Lee et al., 2014). The unit or module in biology is defined as a semiautonomous unit or element that has general homology within a system (Klingenberg et al., 2003; Kuratani, 2009). The skeletal or functional unit is a form with independent and unique

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characteristics which can be used for the evaluation of genetic or developmental association. The functional units for the mandibular structures were elaborately introduced by Moss (Moss, 1968; Moss and Rankow, 1968). Functional unit theory characterizes the mandible as having six distinct skeletal units with its distributing masticatory muscle: the condyle, coronoid, body, angle, dentoalveolus, and symphysis (Moss, 1968; Park et al., 2010) (Fig. 1). Each unit is affected by its surrounding functional matrix, and the overall mandibular growth is a sum of the independent growth of each unit (Moss, 1968; Precious and Delaire, 1987).

HFM structures are known to be affected at the first and/or second pharyngeal arches during embryonic development (Stark and Saunders, 1962; Converse et al., 1973; Wink et al., 2014; Tuin et al., 2015), but the etiologic pathogenesis remains controversial (Cousley and Calvert, 1997; Charrier et al., 2001; Zielinski et al., 2014). The mandible is developed at the first pharyngeal arch by the development of Meckel's cartilage of mesodermal origin and its successive formation of intramembranous bone of mesenchymal origin at the mandibular body region (Ranly, 1988). The embryonic mandible later continues to develop with the formation of secondary cartilages at the condyle, coronoid, and angular region. These subsequently unite with the body region to form one mandibular structure, although each unit retains its characteristics as the masticatory muscles develop and connect to them during the eighth week of gestation (Lee et al., 2001).

After birth, the mandibular bony structure increases in size and changes in shape, mainly due to condylar displacement and superficial bony apposition and resorption (Enlow, 1990; Lee et al., 2001) (Fig. 1a). Meanwhile, the masticatory muscular structure represents another basic component of the musculoskeletal system. It is attached to each skeletal unit of mandible and related to the orientation and form of skeletal structures (Delaire et al., 1981), which can thus be changed by inherent growth capacity as well as by the masticatory muscles and functional activity during postnatal growth (Shibazaki-Yorozuya et al., 2014).

By understanding that the HFM mandible and its masticatory muscles are impaired, we can anticipate a growth pattern different from normal. In order to treat HFM properly, we need to differentiate primary defects of prenatal origin from secondary defects related to growth abnormality. It is therefore important to understand its growth potential as well as the structural characteristics of the affected mandible in the same context. However, their postnatal growth potentials are unclear and even controversial (Nada et al., 2010). Some different surgical modalities and timing for mandibular HFM have been suggested, including early or delayed surgical treatment as well as surgical techniques encompassing orthognathic surgery, distraction ostogenesis and costochondral graft (Kaban et al., 1986, 1988; Munro et al., 1989; Padwa et al., 1998; Bertin et al., 2017).

We therefore wanted to understand the structural characteristics of HFM mandible, especially in terms of skeletal unit, to identify underdeveloped or improperly grown skeletal regions. This will provide information on the region of necessary treatment as well as clues regarding etiopathogenesis. We also hoped to estimate and compare the structural characteristics of HFM mandibular growth by comparing them among different age groups to understand growth potential and to determine a possible treatment schedule.

Here we performed a three-dimensional (3D) skeletal unit analysis of HFM mandibles with computed tomography (CT) images. We identified areas of impaired structure in HFM mandible and compared them with those of normal controls as well as those on the unaffected side, which were also subdivided by age groups. From these results, we derived the 3D architectural characteristics of the HFM mandible for improved diagnosis, growth prediction, and treatment planning.

2. Materials and methods

We studied the CT images of 28 subjects (20 men and 8 women) with unilateral HFM as group II and 27 subjects (11 males and 16 females) of normal control as group I (Table 1). Group II consisted of 13 Korean and 15 French HFM mandibles, and Group I 27 normal Korean mandibles for control. Their ages ranged from 5 to 36 years (mean age 14.8 ± 7.1 years) for HFM, and from 20 to 29 years old (mean age 24.2 ± 2.9 years) for normal controls. We examined the two racial population groups of HFM together only to increase the sample size, as the comparison would have been difficult given the relatively small numbers. Moreover, because we could not get normal control subjects with craniofacial CT images from the French population and young age groups, we had to confine the controls to Korean young adults. In addition, we had wanted to trace the growth of HFM to evaluate the growth potential, but were confined to a cross-sectional evaluation comparing different age groups due to the lack of available data. To evaluate possible distortion due to the selection of samples and controls, we evaluated and compared their basic mandibular structure using statistical methods to confirm that it was worth working with them.

Group I subjects for normal control consisted of Korean young adults with skeletal class I occlusion and normocephalic profile who had undergone CT evaluation for a previous study and whose detailed inclusion criteria could be reviewed in our report (Lee et al., 2014). HFM in group II was diagnosed clinically as well as radiographically. All had mandibular and ear deformities with or without ear canal malformations and were classified into three subgroups, types I, II, and III, mainly based on Pruzansky's classification (Converse et al., 1973; Caldarelli et al., 1980; Wink et al., 2014) by three authors (Lee, Corre and Hellios). HFM with type I in this classification shows mild mandibular hypoplasia, particularly in the condylar and ramal regions, presenting a smaller mandible with balanced proportion and intact morphology. Type II HFM demonstrates more than one deformed mandibular part and resultant unbalanced proportion, but with an articulating temporomandibular joint. Type III represents complete or partial loss of some mandibular structures with a non-functional temporomandibular joint.

We also categorized the subjects into three age groups including child (under 12 years old), adolescent (12–18 years old), and adult (over 18 years old) based on the timing of secondary sex characteristics and mandibular growth maturity (Ranly, 1988; Enlow, 1990). Subjects were diagnosed at the Department of Oral and Maxillofacial Surgery, Dental Hospital, Yonsei University, the Department of Oral and maxillofacial surgery, Daejeon Hospital, Wonkwang University, Korea and Department of Maxillofacial Surgery and Stomatology, Nantes University Hospital, Medical College, Nantes University, France. All these works were approved by the local ethics committee of the Dental College Hospital, Yonsei University, Seoul, Korea and Daejeon Dental Hospital, Wonkwang University, Daejeon, Korea (IRB 2-2011-0016; W1602/001-001), and also followed the ethical guidelines for medical data usage of Nantes University Hospital.

All subjects underwent CT scanning before any surgical treatment to the mandibular area. Most subjects had undergone multidetector CT (MDCT; N = 48) except for some of the French subjects (N = 7/15), who had undergone cone-beam CT (CBCT). For MDCT, subjects were positioned with the Frankfort horizontal line perpendicular to the floor, the facial midline being parallel to the long axis of the CT machine. The imaging was performed with CT machines (Hispeed Advantage, GE Medical Systems, Milwaukee, WI, USA for Korean subjects, and by Sensation 16, Siemens, Erlangen, Germany for French subjects), using a high-resolution bone algorithm for Koreans (200 mA, 120 kV, scanning time of 1 s,

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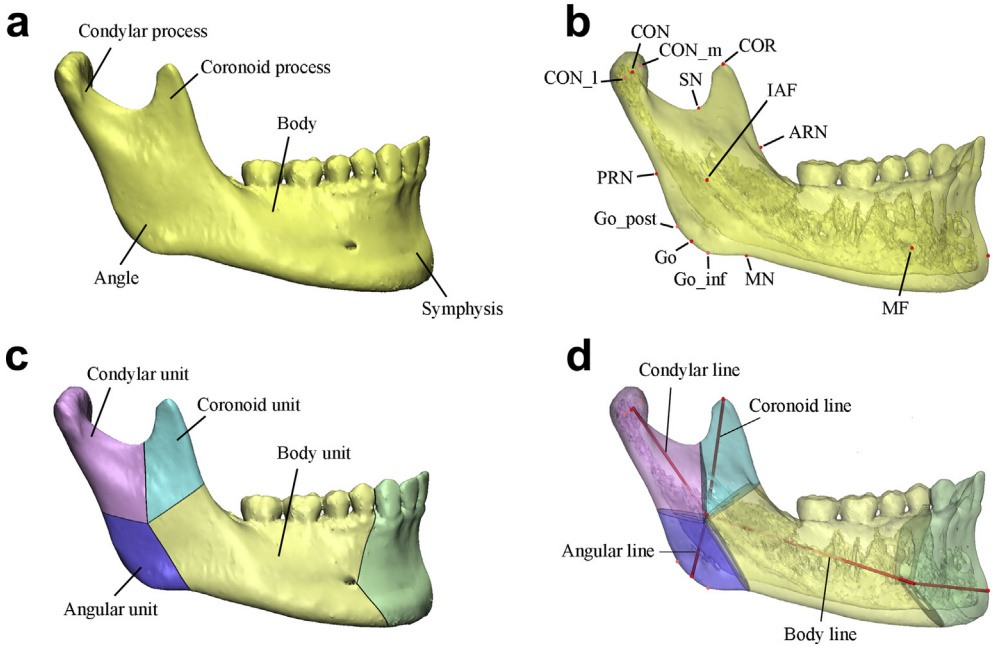

Fig. 1. A normal mandible and its skeletal units from group I (normal). (a) A normal mandible in three-dimensional model from CT data of a group I (normal) subject; (b) designation of reference points for skeletal units; (c) division of mandibular skeletal units; (d) mandibular skeletal units were geometrically delineated by connecting the reference points. Note: Definition of reference points in Fig. 1b: (1) inferior alveolar foramen (IAF): the most inferior point of the inferior alveolar foramen; (2) mental foramen (MF): the most anterior point of the entrance of the mental foramen; (3) condyle_lateral (CON_l): the most lateral point of the mandibular condyle; (4) condyle_medial (CON_m): the most medial point of the mandibular condyle; (5) condyle (CON): the middle point of the condyle_lateral (CON_l) and condyle_medial (CON_m); (6) coronoid (COR): the most superior tip point of the mandibular coronoid process; (7) gonion (Go): the middle point between the most posterior Go point (Go-post) and the most inferior Go point (Go-inf) at the angle of the mandible; (8) sigmoid notch (SN): the deepest point of sigmoind notch between condyle and coronoid; (9) posterior ramal notch (PRN): the most anterior point of posterior ramal notch; (10) anterior ramal notch (ARN): the most posterior point of anterior ramal notch; (11) masseteric notch (MN): the most superior point of gonial (masseteric) notch. Note: Definition of skeletal units in Fig. 1c: (1) condylar unit: the area between CON and IAF, pink; (2) coronoid unit: the area between COR and IAF, blue; (3) angular unit: the area between Go and IAF, purple; (4) body unit: the area between MF and IAF, yellow. Note: Definition of skeletal units in Fig. 1d: (1) condylar unit line from CON to IAF; (2) coronoid unit line from COR to IAF; (3) angular unit line from Go and IAF; (4) body unit line from MF and IAF.

1.00 mm scan thickness, 512 × 512 pixel reconstruction matrix, and 0.48 mm × 0.48 mm × 1.0 mm voxels) or H70h algorithm for French subjects (99.0 mA, 120 kV, scanning time of 1 s, 0.45 mm scan thickness, and 512 × 512 pixel reconstruction matrix). The images were scanned from the cranial vault to the chin. CBCT for French HFM was taken with a NewTom VG MARK3 CBCT scanner (Quantitative Radiology SRL Co., Verona, Italy; standard algorithm, 0.02 mA, 110 kV, 616 × 614 pixels, pixel size 0.25 mm).

The CT image data were saved in DICOM file format, transferred to a personal computer, and reconstructed for 3D mandibular models from CT images with the same Hounsfield unit values for bone setting, using the SimPlant software version 14.0 (Materialise NV, Leuven, Belgium). The reference points for the description of the skeletal units of mandible (Moss and Simon, 1968) were based on our previous studies (Park et al., 2010, 2013; Kim et al., 2017) (Fig. 1) to include the condylar, coronoid, and angular points. The developmental priority of the basal mandible was attributed to the vascular structure, which defined the inferior alveolar and mental foramen. Some structures (such as the condyle or coronoid) of subjects from group II were partly or almost totally missing, such that their reference points had to be approximated. The skeletal unit was set geometrically by connecting each reference point, including the masseteric and sigmoid notch (Fig. 1b,c).

The reference points were connected to make skeletal unit lines for the geometrical representation of each unit (Fig. 1d). Then the lengths of each skeletal unit line and their relative angulations were measured in software as previously reported (Park et al., 2013). Each measurement of the affected and unaffected sides was compared for each age group, and all measurements were statistically analyzed using SPSS 22.0 software (IBM Corp., Armonk, NY, USA). For group I (normal control), the right side was arbitrarily assigned to the affected side. The small number of type I in group II (N = 3) and the absence of subjects from type III adult prevented their statistical comparison.

The possible influence of gender, population, and age on the results was statistically evaluated by chi-square or Kruskal–Wallis test or one-way analysis of variance. The measurements of body unit on the unaffected side for Korean and French populations were compared to evaluate their homogeneous nature in HFM group by the chi-square test. Among the skeletal units of mandible, the body unit was selected for comparison because our preliminary study showed it to be the least affected unit (Choi et al., 2015). In addition, the body unit size for group I was compared with the unaffected

Table 1
Subject profiles.

	Group I	Group II			
	Normal	Type I	Type II	Type III	Subtotal
Gender					
Male	11	3	11	6	20
Female	16	0	7	1	8
Nationality					
Korean	27	1	12	0	13
French	0	2	6	7	15
Age group[a]					
Child	0	2	7	3	12
Adolescent	0	0	5	4	9
Adult	27	1	6	0	7
Total	27	3	18	7	28

[a] Age group: child, ~11 years; adolescent, 12–18 years; adult, 19~ years.

side body unit of type II adult HFM to understand their comparability by post-hoc analysis after Kruskal–Wallis test.

The error level for the reference points was studied by marking the selected reference points three times at an interval of 7 days by two authors (Kim and Lee). Intra- and interobserver reliability was evaluated by Dahlberg's formula and analyzed statistically by intraclass correlation (ICC) with 95% confidence intervals.

3. Results

Statistical analysis for the possible influence of gender on the results showed no significant difference by the chi-square test ($p = 0.427$), while the age and population-related influences did ($p = 0.00$ each, age by Kruskal–Wallis and population by chi-square). HFMs with age tended to show greater measurement values, and French HFM tended to be more severe in phenotype, showing a larger number of type III than Korean HFM.

We compared the measurements of unaffected body units in Korean and French populations to explore the possibility of sorting by age. The statistical analysis showed no statistical difference between Korean and French subjects of type II child, adolescent, or adult HFM in measurements of unaffected body unit ($p = 0.087$ by chi-square test). Measurement comparisons for group I and group II adult showed that the mean body unit size on the unaffected side was 59.3 mm in group II adult and 61.0 mm in group I, which was not significantly different ($p = 0.322$) by the Kruskal–Wallis test.

Based on these findings, we started to evaluate the unit structures and to compare the size discrepancy between the affected and unaffected skeletal units of mandible. The group II consisted of type I ($N = 3$), type II ($N = 18$), and type III ($N = 7$) HFM with different ages (Table 1). There were 12 subjects in the child group, 9 for adolescents, and 7 for adults.

The group I skeletal units were well balanced in terms of shape and proportion, the body unit being the largest and centrally positioned (Table 2 and Fig. 1). The condylar and coronoid units projected superiorly and posteriorly on the similar pattern. The median size of affected and unaffected condylar and body unit in group I (normal) was 39.3 and 39.8 mm (for condyle) and 61.0 and 60.4 mm (for body) (Table 2). There were no significant differences between the affected and unaffected sides ($p = 0.556$ for condyle and $p = 0.566$ for body by two paired t-test). The affected and unaffected coronoid or angular units of group I were not significantly different as well.

However, group II (HFM) units were markedly different in shape and size (Fig. 2). The condylar and angular unit, especially from type III, was smaller, more deformed, and sometimes vestigial in shape (Fig. 2j,l). The coronoid unit was relatively less deformed than the condylar and angular units in type II and III (Fig. 2e–l). The body units of type II and III were consistently greater and much less deformed, retaining their normal plump and straight shape relative to units.

Comparative measurements of skeletal units were confined to Group I (normal) and type II and III of Group II HFM, as previously described. The comparison of affected and unaffected mandibular units showed the greatest difference at the condylar unit ($p = 0.00$ by two sample t-test), followed by the coronoid and body units (Table 2, Fig. 2). Almost all units in type II HFM were greater than those in type III (Table 2). Moreover, the unaffected side of type II showed the greater size for all skeletal units as the group age increased. The unit size of type II adult was similar to the size of group I as previously described. Also, the condylar and coronoid units of the affected side in type II increased with age, in contrast to the body and angular units. In addition, type III HFM did not show greater unit size by age group.

The median size of condylar unit on the affected side of group II was 24.1 mm (type II child), 25.3 mm (type II adolescent), 32.6 mm (type II adult), 10.1 mm (type III child), and 12.4 mm (type III adolescent), while that of the unaffected side was 35.0 mm, 35.3 mm, 39.3 mm, 34.4 mm, and 33.3 mm for the same subgroups (Table 2 and Fig. 2). Thus the condylar unit size discrepancy between the affected and unaffected side reached 6.7–10.9 mm for type II and exceeded 20 mm for type III. In addition, the condylar unit size of the affected side in type II and III child and adolescent, but not type II adult, was significantly different from that of group I by the Kruskal–Wallis test.

The coronoid unit size of the affected side was 30.5 mm (type II child), 35.8 mm (type II adolescent), 36.3 mm (type II adult), 13.4 mm (type III child) and 18.0 mm (type III adolescent) in median value, while the unaffected side was 32.0 mm, 40.4 mm, 41.3 mm, 38.4 mm and 35.0 mm (Table 2 and Fig. 2). The coronoid unit size of the affected side in type II child as well as type III child and adolescent was significantly different from that of group I, but that of type II adult and adolescent was not. Also, the size discrepancy of coronoid unit between the affected and unaffected side was 1.5–5 mm for type II and 17.0–25.0 mm for type III.

The median body unit size on the affected side was 49.0 mm (type II child), 52.7 mm (type II adolescent), 48.3 mm (type II adult),

Table 2
Length of mandibular skeletal units for group I (normal) and group II (hemifacial microsomia).

	Side	Group I	Group II					p[a]
			II ch	II ado	II adu	III ch	III ado	
Condyle	n-Aff.	39.8	35	35.3	39.3	34.4	33.3	I≠II ch, II ado, III ado
	Aff.	39.3	24.1	25.3	32.6	10.1	12.4	I≠II ch, II ado, III ch, III ado
	diff.	0.5	10.9	10.0	6.7	24.3	20.9	
Body	n-Aff.	61	50.4	58.9	59.3	53.8	58.7	I≠II ch
	Aff.	60.4	49	52.7	48.3	39.6	42.4	I≠II ch, III ch, III ado
	diff.	0.6	1.4	6.2	11.0	14.2	16.3	
Coronoid	n-Aff.	42.8	32	40.4	41.3	38.4	35.0	I≠II ch
	Aff.	41.3	30.5	35.8	36.3	13.4	18.0	I≠II ch, III ch, III ado
	diff.	1.5	1.5	4.6	5.0	25.0	17.0	
Angle	n-Aff.	23.6	17.4	22	22.7	17.8	19.5	I≠II ch
	Aff.	24.0	16.8	23.1	16.6	20.0	18.4	
	diff.	−0.4	0.6	−1.1	6.1	−2.2	1.1	

All values expressed as median (mm).
II ch: type II child, II ado: type II adolescent, II adu: type II adult, III ch: type III child, III ado: type III adolescent.
n-Aff.: non-affected side, Aff.: affected side, diff.: difference between the non-affected side and affected side.
Type I of group II HFM was not included for length measurement analysis only due to the small sample size ($N = 3$).
[a] p by Kruskal–Wallis test and statistically significant ($p < 0.05$).

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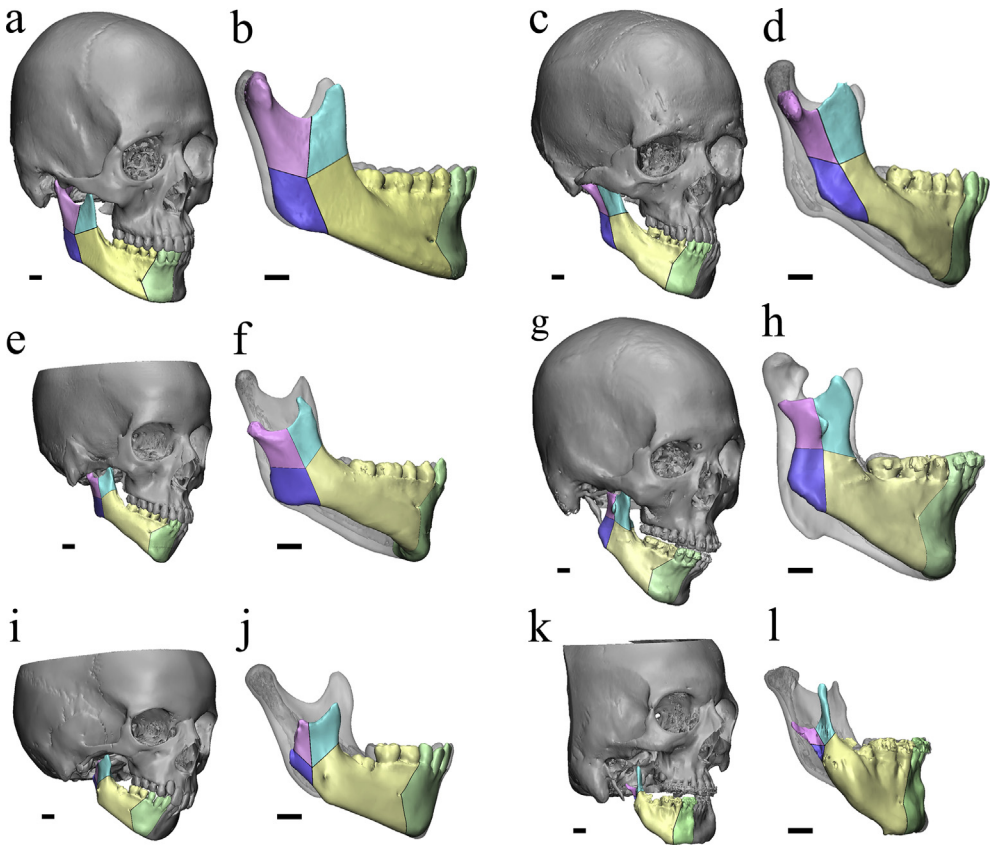

Fig. 2. The comparison of skull and mandible of group I (normal) and group II (hemifacial microsomia [HFM]) with the mandibular skeletal units in different age groups. (a, b) Normal adult skull and mandible from group I with well-balanced size and morphology of skeletal units. (c, d) Type I adult HFM skull and mandible, with small-sized, but morphologically intact condylar and angular units. (e, f) Affected side of type II child HFM skull and mandible, showing the reduced size of condylar, coronoid, and angular unit with preserved morphology. (g, h) The adult skull and mandible of type II HFM, showing deformed and smaller condylar, coronoid, and angular unit, with the articulating temporomandibular joint. (i, j) Affected skull and mandible of child type III HFM, with markedly smaller and deformed condylar and angular units and a small coronoid process. (k, l) The skull and mandible from adolescent-type III HFM, with severely deformed condylar, coronoid, and angular units and also small body unit. Note: pink for condylar unit; blue for coronoid; purple for angular; and yellow for body. The unaffected side of mandible is shown in gray at the back side of HFM-affected side mandible, which was subdivided into skeletal units in Fig 2b, d, f, h, j, and l. The bar in the figures indicates 5 cm for the skull and 1 cm for the mandible.

39.6 mm (type III child), and 42.4 mm (type III adolescent), while the unaffected size was 50.4 mm, 58.9 mm, 59.3 mm, 53.8 mm, and 58.7 mm (Table 2 and Fig. 2). The size difference between the affected and unaffected body unit was 1.4–11.0 mm for type II and 14.2–16.3 mm for type III, the statistical difference for body unit between group I and II being the same as those of coronoid. The affected angular units of groups I and II showed no significant differences. Furthermore, the difference between the affected and unaffected side was −1.1 to 6.1 mm for type II and −2.2 to 1.1 mm for type III.

The angulation between the affected and the unaffected skeletal units was also evaluated (Table 3), The angles formed between the affected and unaffected units in group I were less than 3.7°, except for the angular unit, which was 7.8°. Angles in group II differed significantly, exceeding 8.7° in all the mandibular skeletal units, the angle of type III being greater than that of type II.

Almost all angles in type II adult were smaller than those of child and adolescent except for the angular unit (Table 3). Also, the condylar and body units in type II and III showed a tendency toward decreased angulation between the affected and unaffected side with age, unlike angular and coronoid units. Moreover, the difference in angulation between group I and type II adult of group II was 6.2–8.4°, not significantly different except for the coronoid unit.

The angles formed in type III HFM differed significantly from those of group I, exceeding about 20°, except for the angular unit (Table 3). In addition, the body unit in the adolescent group showed an angle of 37.2°, as compared with 2.5° in group I. The angular unit in type II and type III showed relatively similar angles in all age groups, ranging 26.0–33.1°.

When we evaluated the error levels of selected reference points for method errors, none of the measurements were significantly different statistically, with differences of 0.21 mm for CON, 0.32 mm for COR, and 0.24 mm for MF in 3D distances (detailed data not shown). The ICC with a 95% confidence interval was found to be 0.967 ($p > 0.001$) for intraobserver reliability, and 0.902 ($p > 0.001$) for interobserver reliability.

4. Discussion

HFM is the second most common congenital syndrome on the face after the cleft lip and palate (Meazzini et al., 2005; Ahiko et al., 2015; Tuin et al., 2015), its prevalence ranging from 1:3,500 to 1:26,550 live births (Poswillo, 1974; Melnick, 1980). The phenotypic expressions of HFM occur unilaterally, but 10%–33% of cases present bilateral involvement (Grabb, 1965; Rollnick et al., 1987; Ahiko et al., 2015), their correlation remaining uncertain.

The pathogenesis of HFM is also unclear. One hypothesis suggested a disruption of the stapedial artery (Poswillo, 1973, 1975), which supplies the first and second brachial arch and the rupture of which can lead to the formation of a hematoma and subsequent

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Table 3
Angles formed between the affected and unaffected skeletal units of group I (normal) and group II (hemifacial microsomia).

	Group I	Group II					p[a]
		II ch	II ado	II adu	III ch	III ado	
Condyle	2.5	20.3	16.1	8.7	46.4	28.3	I≠II ch, III ch, III ado
Body	2.5	16.4	16.6	10.4	42.7	37.2	I≠II ch, II ado, III ch, III ado
Coronoid	3.7	14.1	9.7	12.1	29.6	48.1	I≠II ch, II adu, III ch, III ado
Angle	7.8	26.7	26.5	33.1	26.7	26	I≠II ch, II ado, II adu

All values expressed as degrees.
II ch: type II child, II ado: type II adolescent, II adu: type II adult, III ch: type III child, III ado: type III adolescent.
n-Aff.: non-affected side, Aff.: affected side, diff.: difference between the non-affected side and affected side.
Type I of group II HFM was not included for length measurement analysis only due to the small sample size ($N = 3$).
[a] p by Kruskal–Wallis test and statistically significant ($p < 0.05$).

deformation of surrounding tissues. Another hypothesis proposes that the abnormal migration of the cranial neural crest cell subpopulation leads to abnormal craniofacial development and dysmorphogenesis (Johnston and Bronsky, 1995; Kallen et al., 2004; Heude et al., 2011). However, despite considerable interest in the pathogenesis of HFM, the cause remains unclear.

Also uncertain is the growth potential of the HFM mandible. Some authors have reported that HFM patients showed a more distinct asymmetry after the growth, as the unaffected side grows faster (Murray et al., 1984; Kaban et al., 1986; Padwa et al., 1998). However, others have suggested that the degree of facial asymmetry does not accelerate during growth (Vargervik et al., 1986; Polley et al., 1997; Marquez et al., 2000; Huisinga-Fischer et al., 2003; Sarnas et al., 2004; Meazzini et al., 2005). Recent studies mainly favor the latter characterization, based on radiographic follow-up or literature review (Mommaerts and Nagy, 2002; Huisinga-Fischer et al., 2003; Sarnas et al., 2004; Meazzini et al., 2005; Chow et al., 2008; Nagy et al., 2009; Bartlett, 2010; Pluijmers et al., 2014). However, most of these studies focused mainly on postgraft- or postdistraction-related surgical relapse by comparing outcomes with presurgical conditions. Even though we fully acknowledge the limitations of cross-sectional comparison by individual variation due to lack of a pure population or exaggerated geometrical simplification of structure, we intended to compare HFM by age groups in order to compensate for limitations of archival HFM growth data.

Also, clinicians differ regarding the proper timing, and clinical management of HFM also varies by clinicians, their opinions mainly correlating with their views on the growth potential (Nada et al., 2010). Advocates of early surgical intervention point to the early improvement of bone density, stimulation of growth, and decreased malocclusion (Converse et al., 1973; Kaban et al., 1986; Ohtani et al., 2012). However, supporters of delayed treatment prefer to take advantage of the growth potential of HFM and to avoid growth impairment due to early intervention (Polley et al., 1997; Nagy et al., 2009). Long-term studies after distraction osteogenesis reported limited vertical bone growth, reduced growth ratio of the affected side, or relapse (Marquez et al., 2000; Huisinga-Fischer et al., 2003; Meazzini et al., 2005, 2008).

The main treatment goal for HFM needs to focus on the restoration of normal function and structure as well as the induction of normal growth. Deformed mandible of HFM can be characterized by the simultaneous involvement of proximal mandibular bony structure and its masticatory muscles. This was our starting point in analyzing HFM in terms of skeletal units. We conducted a preliminary study of HFM skeletal units using 3D CT (Choi et al., 2015). Even with its small number of subjects, this study showed the main contribution of the condylar unit to HFM-induced facial asymmetry, thus demonstrating the usefulness of skeletal unit analysis for HFM. In addition to skeletal unit analysis, 3D data analysis can be helpful for HFM diagnosis and treatment planning, especially when the decision requires information on direction as well as length control (Kunz et al., 2003; Takahashi-Ichikawa et al., 2013).

We thus sought out underdeveloped and/or improperly grown skeletal regions of the mandible in order to understand the structural characteristics of HFM. We first tried to analyze the size of unaffected skeletal units in HFM mandible. Those unaffected units of adult or adolescent group in type II and III were not significantly different from those of group I as an adult normal control. In addition, the size of unaffected units increased with age. Although we admit the limitation of this study in terms of its cross-sectional nature, these results basically showed that the skeletal units of the unaffected side in type II or III could be as large as normal ones.

In addition, there was no evidence for unaffected units being larger than normal ones, indicating the lack of evidence for the possible overgrowth of unaffected units, as was proposed in a previous study (Chow et al., 2008). Our search of the literature found no studies on the growth of unaffected HFM mandible aside from a report by Huisinga-Fischer et al. (2003), which described the continuous growth of the unaffected mandible after distraction osteogenesis.

The affected unit sizes were also analyzed. They were significantly smaller in group II than in group I ($p < 0.05$), except for type II adult (for condylar, body and coronoid units). In addition, affected condylar and coronoid units were larger with age, unlike the body and angular units. These results suggest that the skeletal units of affected side in type II, not in type III, could be as large as normal units of group I. They also raise the possibility that the affected condylar and coronoid units have more growth potential than the body and angular units.

HFM growth studies have focused mainly on the progression of asymmetry, but few have investigated regional growth of HFM mandible. Polley et al. (1997) and Kunsto et al. (Kusnoto et al., 1999) demonstrated that the growth of affected sides of mandibles in untreated HFMs parallel those of the unaffected sides, especially at the vertical ramus and the body length.

The differential analysis of unit size between the affected and unaffected side lends insight into the etiopathogenesis of HFM. The difference was greatest at the condylar unit, followed by the coronoid unit. Specifically, the body, coronoid, and angular units in type II child showed unit differences less than 2.0 mm, in contrast to 10.9 mm for the condylar unit. This condylar unit discrepancy decreased to as little as 6 mm, while the differential in other units increased with group age. The results were similar for type III, which showed the greatest difference at the condylar and coronoid units.

These results thus suggest that the condylar unit for type II and condylar/coronoid unit for type III might be more influenced by the prenatal pathologic process of HFM. On the other hand, the body and angular unit are more disturbed by the growth process and/or the functional activity of HFM. Shibazaki-Yorozuya et al. (2014)

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recently reported on their CBCT analysis of HFM growth over 2–4 years, but their measurement parameters, being based on the Frankfort plane or midsagittal plane, can hardly be correlated with ours. According to them, the ramal vertical growth rate was slower than that on unaffected side, and the body length was variable. These data are less specific than those in previous studies using cephalometric radiographs (Polley et al., 1997; Kusnoto et al., 1999; Sarnas et al., 2004).

Even given the possible normal size on the unaffected side of HFM, angulation can give rise to a different issue. Our results show that the angulations between the affected and unaffected skeletal units in type II were smaller than those of type III, but greater than those of group I. Almost all skeletal units in types II and III showed significant differences in angulation from those of group I, except for the adult group of type II. The child age group showed greater angulation than did the older age groups, the angulation decreasing with age. Thus the angulation perhaps improves toward the normal level during type II growth. On the other hand, type II still presents more than 6 degrees of angulation as compared with group I, and type III was more than 18°. These greater angulations may be related to the severity of HFM, especially in cases of asymmetry, and require our consideration in terms of controlling direction, as well as augmentation for insufficient size.

A basic question thus arises from these results regarding the major contribution of condylar and coronoid units to HFM. We have no evidence on the preference of HFM to the condylar unit and its adjacent region except for a report on the stapedial artery, which was suggested as the main cause of HFM by Poswillo (Poswillo, 1973, 1975). It is transiently present during embryonic development and atrophies at the third gestational month (Rodriguez-Vazquez, 2005). The maxillomandibular branch of persistent stapedial artery exits the cranium at the foramen spinosum and makes the mandibular (or later inferior alveolar artery) and infraorbital artery (Silbergleit et al., 2000). Animal experimental data on the stapedial artery and the developmental and anatomical vicinity of the condylar and coronoid development (as secondary cartilage) suggest the possibility of HFM's main involvement at the condylar region.

The body or angular unit seemed different from the condylar/coronoid unit in terms of etiopathogenesis as well as the influence of growth. As muscular architecture represents a basic structure and particularly involves the orientation and form of skeletal structures (Delaire et al., 1981), the small size of body or angular unit seemed to be more related to the limited function of the affected side and its attached masticatory muscles. Several authors report that the lack of masticatory muscle is related to underdevelopment in HFM (Vargervik and Miller, 1984; Marsh et al., 1989; Huisinga-Fischer et al., 2001). However, the volume of HFM masticatory muscle was not consistently related to the degree of deformity (Kane et al., 1997). Different patterns of chewing among HFM subjects may constitute a variable in unit size discrepancy. Further detailed studies are needed to determine the relationship between mandibular skeletal units and masticatory muscles and their contribution to the differential growth of skeletal units.

Based on the results of this study, we can treat HFM mandible through the differential application of distraction osteogenesis or other surgical techniques. These can target specific regions, i.e., skeletal units, and also specific dimension of size or angle. Any technique can be optimized to lengthen the short units, whether condylar, body, or even the angular unit, and to correct the angles of the units for the restoration of the normal skeletal structure. Also, a way must be found to lengthen or activate the surrounding muscles and periosteum for the construction of healthy skeletal units.

Regarding treatment timing, this study indicates that the type II skeletal units tend to have more normal structure, while type III does not. Moreover, the growth after surgical treatment, including costochondral graft, distraction, or bimaxillary surgeries (Munro et al., 1989; Kusnoto et al., 1999; Sarnas et al., 2004), generally showed variable patterns, with some relapse tendency. The functional activator treatment can induce, either totally or partially, balanced maxillomandibular growth (Kahl-Nieke and Fischbach, 1998). Based on the finding that the condylar unit in type II had better growth potential even up to the level of normal condylar structure, we can focus on treatment and/or education to accomplish active functional exercise before the completion of condylar growth. On the other hand, the growth potential of body and angular unit in type II was inferior to that of the condylar skeletal unit, mildly so initially but becoming more severe with age. We thus may be able to introduce some conservative treatment, such as orthodontic treatment or functional orthopedic appliances, so as not to damage but to encourage the growth potential of the units before the completion of growth. For type III mandible, the growth potential is not evident, and the magnitude of diminished size with poor angulation is great. Early surgical treatment must therefore compensate for all structural drawbacks based on the concept of skeletal units and their working matrix.

5. Conclusion

Our study evaluated 3D structural characteristics and growth potential of HFM mandible in terms of skeletal units. The results showed that HFM mainly affected the condylar unit (for type II) or condylar/coronoid unit (for type III), with improvement with age in type II. The angulation between the skeletal units in type II tended toward normalcy with age, although not in type III. Mandibular skeletal unit analysis may be a useful tool for individualized diagnosis, identification of the major etiopathogenic area, and treatment planning, including a simulation to set up a reconstruction regimen for successful reconstruction of HFM.

Conflicts of interest

We declare that we have no conflict of interest.

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References

Ahiko N, Baba Y, Tsuji M, Suzuki S, Kaneko T, Kindaichi J, et al: Investigation of maxillofacial morphology and dental development in hemifacial microsomia. Cleft Palate Craniofac J 52: 203–209, 2015

Bartlett SP: No evidence for long-term effectiveness of early osteodistraction in hemifacial microsomia. Plast Reconstr Surg 125: 1567–1568, 2010

Bertin H, Mercier J, Cohen A, Giordanetto J, Cohen N, Lee SH, et al: Surgical correction of mandibular hypoplasia in hemifacial microsomia: a retrospective study in 39 patients. J Craniomaxillofac Surg 45: 1031–1038, 2017

Caldarelli DD, Hutchinson Jr JG, Pruzansky S, Valvassori GE: A comparison of microtia and temporal bone anomalies in hemifacial microsomia and mandibulofacial dysostosis. Cleft Palate J 17: 103–110, 1980

Charrier JB, Bennaceur S, Couly G: Hemifacial microsomia. Embryological and clinical approach. Ann Chir Plast Esthet 46: 385–399, 2001

Choi JW, Kim BH, Kim HS, Yu TH, Kim BC, Lee SH: Three-dimensional functional unit analysis of hemifacial microsomia mandible–a preliminary report. Maxillofac Plast Reconstr Surg 37: 28, 2015

Chow A, Lee HF, Trahar M, Kawamoto H, Vastardis H, Ting K: Cephalometric evaluation of the craniofacial complex in patients treated with an intraoral distraction osteogenesis device: a long-term study. Am J Orthod Dentofacial Orthop 134: 724–731, 2008

Converse JM, Coccaro PJ, Becker M, Wood-Smith D: On hemifacial microsomia. The first and second branchial arch syndrome. Plast Reconstr Surg 51: 268–279, 1973

Cousley RR, Calvert ML: Current concepts in the understanding and management of hemifacial microsomia. Br J Plast Surg 50: 536–551, 1997

Delaire J, Schendel SA, Tulasne JF: An architectural and structural craniofacial analysis: a new lateral cephalometric analysis. Oral Surg Oral Med Oral Pathol 52: 226–238, 1981
Enlow D: Facial growth, 3rd ed. Philadelphia, PA: Saunders, 1990
Figueroa AA, Pruzansky S: The external ear, mandible and other components of hemifacial microsomia. J Maxillofac Surg 10: 200–211, 1982
Gougoutas AJ, Singh DJ, Low DW, Bartlett SP: Hemifacial microsomia: clinical features and pictographic representations of the OMENS classification system. Plast Reconstr Surg 120: 112e–120e, 2007
Grabb WC: The first and second branchial arch syndrome. Plast Reconstr Surg 36: 485–508, 1965
Grayson BH, Boral S, Eisig S, Kolber A, McCarthy JG: Unilateral craniofacial microsomia. Part I. Mandibular analysis. Am J Orthod 84: 225–230, 1983
Heude E, Rivals I, Couly G, Levi G: Masticatory muscle defects in hemifacial microsomia: a new embryological concept. Am J Med Genet A 155A: 1991–1995, 2011
Huisinga-Fischer CE, Zonneveld FW, Vaandrager JM, Prahl-Andersen B: Relationship in hypoplasia between the masticatory muscles and the craniofacial skeleton in hemifacial microsomia, as determined by 3-D CT imaging. J Craniofac Surg 12: 31–40, 2001
Huisinga-Fischer CE, Vaandrager JM, Prahl-Andersen B: Longitudinal results of mandibular distraction osteogenesis in hemifacial microsomia. J Craniofac Surg 14: 924–933, 2003
Johnston MC, Bronsky PT: Prenatal craniofacial development: new insights on normal and abnormal mechanisms. Crit Rev Oral Biol Med 6: 368–422, 1995
Kaban LB, Moses MH, Mulliken JB: Correction of hemifacial microsomia in the growing child: a follow-up study. Cleft Palate J 23(Suppl. 1): 50–52, 1986
Kaban LB, Moses MH, Mulliken JB: Surgical correction of hemifacial microsomia in the growing child. Plast Reconstr Surg 82: 9–19, 1988
Kahl-Nieke B, Fischbach R: Effect of early orthopedic intervention on hemifacial microsomia patients: an approach to a cooperative evaluation of treatment results. Am J Orthod Dentofacial Orthop 114: 538–550, 1998
Kallen K, Robert E, Castilla EE, Mastroiacovo P, Kallen B: Relation between oculo-auriculo-vertebral (OAV) dysplasia and three other non-random associations of malformations (VATER, CHARGE, and OEIS). Am J Med Genet A 127A: 26–34, 2004
Kane AA, Lo LJ, Christensen GE, Vannier MW, Marsh JL: Relationship between bone and muscles of mastication in hemifacial microsomia. Plast Reconstr Surg 99: 990–997, 1997 discussion 998-999
Kim HJ, Park KM, Tak HJ, Choi JW, Kang SH, Park W, et al: Three-dimensional growth pattern of the rat mandible revealed by periodic live micro-computed tomography. Arch Oral Biol 87: 94–101, 2017
Klingenberg CP, Mebus K, Auffray JC: Developmental integration in a complex morphological structure: how distinct are the modules in the mouse mandible? Evol Dev 5: 522–531, 2003
Kunz C, Brauchli L, Moehle T, Rahn B, Hammer B: Theoretical considerations for the surgical correction of mandibular deformity in hemifacial microsomia patients using multifocal distraction osteogenesis. J Oral Maxillofac Surg 61: 364–368, 2003
Kuratani S: Modularity, comparative embryology and evo-devo: developmental dissection of evolving body plans. Dev Biol 332: 61–69, 2009
Kusnoto B, Figueroa AA, Polley JW: A longitudinal three-dimensional evaluation of the growth pattern in hemifacial microsomia treated by mandibular distraction osteogenesis: a preliminary report. J Craniofac Surg 10: 480–486, 1999
Lee SH, Kil TJ, Park KR, Kim BC, Kim JG, Piao Z, et al: Three-dimensional architectural and structural analysis–a transition in concept and design from Delaire's cephalometric analysis. Int J Oral Maxillofac Surg 43: 1154–1160, 2014
Lee SK, Kim YS, Oh HS, Yang KH, Kim EC, Chi JG: Prenatal development of the human mandible. Anat Rec 263: 314–325, 2001
Marquez IM, Fish LC, Stella JP: Two-year follow-up of distraction osteogenesis: its effect on mandibular ramus height in hemifacial microsomia. Am J Orthod Dentofacial Orthop 117: 130–139, 2000
Marsh JL, Baca D, Vannier MW: Facial musculoskeletal asymmetry in hemifacial microsomia. Cleft Palate J 26: 292–302, 1989
Meazzini MC, Mazzoleni F, Gabriele C, Bozzetti A: Mandibular distraction osteogenesis in hemifacial microsomia: long-term follow-up. J Craniomaxillofac Surg 33: 370–376, 2005
Meazzini MC, Mazzoleni F, Bozzetti A, Brusati R: Does functional appliance treatment truly improve stability of mandibular vertical distraction osteogenesis in hemifacial microsomia? J Craniomaxillofac Surg 36: 384–389, 2008
Melnick M: The etiology of external ear malformations and its relation to abnormalities of the middle ear, inner ear, and other organ systems. Birth Defects Orig Artic Ser 16: 303–331, 1980
Mommaerts MY, Nagy K: Is early osteodistraction a solution for the ascending ramus compartment in hemifacial microsomia? A literature study. J Cranio-Maxillofac Surg 30: 201–207, 2002
Moss ML: A theoretical analysis of the functional matrix. Acta Biotheor 18: 195–202, 1968
Moss ML, Rankow RM: The role of the functional matrix in mandibular growth. Angle Orthod 38: 95–103, 1968
Moss ML, Simon MR: Growth of the human mandibular angular process: a functional cranial analysis. Am J Phys Anthropol 28: 127–138, 1968
Munro IR, Phillips JH, Griffin G: Growth after construction of the temporomandibular joint in children with hemifacial microsomia. Cleft Palate J 26: 303–311, 1989
Murray JE, Kaban LB, Mulliken JB: Analysis and treatment of hemifacial microsomia. Plast Reconstr Surg 74: 186–199, 1984
Nada RM, Sugar AW, Wijdeveld MG, Borstlap WA, Clauser L, Hoffmeister B, et al: Current practice of distraction osteogenesis for craniofacial anomalies in Europe: a Web based survey. J Craniomaxillofac Surg 38: 83–89, 2010
Nagy K, Kuijpers-Jagtman AM, Mommaerts MY: No evidence for long-term effectiveness of early osteodistraction in hemifacial microsomia. Plast Reconstr Surg 124: 2061–2071, 2009
Neiva C, Dakpe S, Davrou J, Diner PA, Devauchelle B, Vazquez MP, et al: Anatomical study of the course of the inferior alveolar nerve in craniofacial microsomia using three-dimensional computed tomography: correlation with the Pruzansky classification. Br J Oral Maxillofac Surg 53: 426–429, 2015
Ohtani J, Hoffman WY, Vargervik K, Oberoi S: Team management and treatment outcomes for patients with hemifacial microsomia. Am J Orthod Dentofacial Orthop 141: S74–S81, 2012
Padwa BL, Mulliken JB, Maghen A, Kaban LB: Midfacial growth after costochondral graft construction of the mandibular ramus in hemifacial microsomia. J Oral Maxillofac Surg 56: 122–127, 1998 discussion 127-128
Park KR, Park HS, Piao Z, Kim MK, Yu HS, Seo JK, et al: Three-dimensional vector analysis of mandibular structural asymmetry. J Craniomaxillofac Surg 41: 338–344, 2013
Park W, Kim BC, Yu HS, Yi CK, Lee SH: Architectural characteristics of the normal and deformity mandible revealed by three-dimensional functional unit analysis. Clin Oral Investig 14: 691–698, 2010
Pluijmers BI, Caron CJ, Dunaway DJ, Wolvius EB, Koudstaal MJ: Mandibular reconstruction in the growing patient with unilateral craniofacial microsomia: a systematic review. Int J Oral Maxillofac Surg 43: 286–295, 2014
Polley JW, Figueroa AA, Liou EJ, Cohen M: Longitudinal analysis of mandibular asymmetry in hemifacial microsomia. Plast Reconstr Surg 99: 328–339, 1997
Poswillo D: The pathogenesis of the first and second branchial arch syndrome. Oral Surg Oral Med Oral Pathol 35: 302–328, 1973
Poswillo D: Otomandibular deformity: pathogenesis as a guide to reconstruction. J Maxillofac Surg 2: 64–72, 1974
Poswillo D: Hemorrhage in development of the face. Birth Defects Orig Artic Ser 11: 61–81, 1975
Precious D, Delaire J: Balanced facial growth: a schematic interpretation. Oral Surg Oral Med Oral Pathol 63: 637–644, 1987
Ranly D: A synopsis of craniofacial growth, 2nd ed. Norwalk, CT: Appleton & Lange, 1988
Rodriguez-Vazquez JF: Development of the stapes and associated structures in human embryos. J Anat 207: 165–173, 2005
Rollnick BR, Kaye CI, Nagatoshi K, Hauck W, Martin AO: Oculoauriculovertebral dysplasia and variants: phenotypic characteristics of 294 patients. Am J Med Genet 26: 361–375, 1987
Sarnas KV, Rune B, Aberg M: Maxillary and mandibular displacement in hemifacial microsomia: a longitudinal roentgen stereometric study of 21 patients with the aid of metallic implants. Cleft Palate Craniofac J 41: 290–303, 2004
Shibazaki-Yorozuya R, Yamada A, Nagata S, Ueda K, Miller AJ, Maki K: Three-dimensional longitudinal changes in craniofacial growth in untreated hemifacial microsomia patients with cone-beam computed tomography. Am J Orthod Dentofacial Orthop 145: 579–594, 2014
Silbergleit R, Quint DJ, Mehta BA, Patel SC, Metes JJ, Noujaim SE: The persistent stapedial artery. AJNR Am J Neuroradiol 21: 572–577, 2000
Stark RB, Saunders DE: The first branchial syndrome. The oral-mandibular-auricular syndrome. Plast Reconstr Surg Transplant Bull 29: 229–239, 1962
Takahashi-Ichikawa N, Susami T, Nagahama K, Ohkubo K, Okayasu M, Uchino N, et al: Evaluation of mandibular hypoplasia in patients with hemifacial microsomia: a comparison between panoramic radiography and three-dimensional computed tomography. Cleft Palate Craniofac J 50: 381–387, 2013
Tuin AJ, Tahiri Y, Paine KM, Paliga JT, Taylor JA, Bartlett SP: Clarifying the relationships among the different features of the OMENS+ classification in craniofacial microsomia. Plast Reconstr Surg 135: 149e–156e, 2015
Vargervik K, Miller AJ: Neuromuscular patterns in hemifacial microsomia. Am J Orthod 86: 33–42, 1984
Vargervik K, Ousterhout DK, Farias M: Factors affecting long-term results in hemifacial microsomia. Cleft Palate J 23(Suppl. 1): 53–68, 1986
Wink JD, Goldstein JA, Paliga JT, Taylor JA, Bartlett SP: The mandibular deformity in hemifacial microsomia: a reassessment of the Pruzansky and Kaban classification. Plast Reconstr Surg 133: 174e–181e, 2014
Zielinski D, Markus B, Sheikh M, Gymrek M, Chu C, Zaks M, et al: OTX2 duplication is implicated in hemifacial microsomia. PLoS One 9: e96788, 2014

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