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Discrepancy in Mandibular Medullary Cavity on Different Sides: More Hints Towards Understanding Hemifacial Microsomia

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Abstract: The authors attempt to approach hemifacial microsomia with macroscopic techniques and look for a link between clinical manifestations with pathogenesis. In this study, for the first time mandibular medullary cavities as essential parts of the mandible were intravitally measured based on the 3-dimensional models. A total of 153 patients were included. The 3-dimensional models of patients' mandibles were reconstructed and medullary cavity volumes (mm^3) were measured. The ratio of medullary cavity volume to mandible volume was calculated to determine the proportion of the marrow in the bone. Statistical significance was found in mandible volumes ($P < 0.001$) and medullary cavity volumes ($P < 0.001$) on different sides. Medullary cavity volumes were significantly related to mandible volumes on both sides (both $P < 0.001$). Medullary cavity volumes on the nonaffected and affected side were both in correlation with age but in different degrees ($r = 0.214$, $P = 0.008$ versus $r = 0.170$, $P = 0.036$). The ratios of medullary cavity volume and the mandible were significantly different ($P < 0.001$) on 2 sides. The volume ratio on the nonaffected side correlated to age while this correlation did not exist on the affected side ($r = 0.195$, $P = 0.016$ versus $r = 0.129$, $P = 0.112$). A smaller medullary cavity found on the affected side could lead to a reduced amount of bone marrow cells and consequently reduced osteogenic and hematopoietic potential. This could result in abnormal bone formation on the affected side of mandible. Proportions of marrow in bone on the affected side irrelevant to patients' ages signify a poorer potential of expansion. This may explain a higher reluctancy of growth in affected mandibular sides.

Key Words: 3-Dimensional measurement, hemifacial microsomia, mandible volume, medullary cavity

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This study has been approved by the ethic committee of Shanghai Ninth People's hospital (2016-156-T105) and carried out under the World Medical Association Declaration of Helsinki (2013 amended version).

The authors affirm that patients agreed with disclosure of anonymous data while signing for operations.

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Hemifacial microsomia (HFM) is one of the most extensive congenital craniofacial deformities. Its definition or essential clinical findings vary between sporadic and syndromic phenotypes, yet there has been a wide consensus on the presence of mandibular and auricular hypoplasia on at least 1 side.[1] Although there are numerous additional symptoms mentioned in literatures or the modified OMENS classification system for HFM, namely malformation of the maxilla,[2] orbits, eyes, facial soft tissues,[3] and even abnormalities of the brain, nerves, the heart, kidneys, and the spine.[4] Patients, especially those of severe HFM classified into Pruzansky-Kaban types II and III, have to live with asymmetrical or distorted facial appearances since their birth, suffering from consequent occlusional dysfunction and impacted social fitness.[5]

Unfortunately, an intact picture about HFM remains veiled. Many studies focused on exploration of its pathogenesis and reached to some mutation sites from genetic sequencing results,[4,6,7] yet limited in vivo and in vitro evidence were shown to further relate these mutations with a regulating pathway of craniofacial developments. Macroscopic clues could be overlooked with views confined microscopically to functions of a single gene. Scholars became aware that researches on HFM may find a way out from a different perspective—1 switched from upstream to downstream. Their attempts to approach HFM with new measurement techniques have made progress on

macroscopically understanding this disease. Tokura et al's[8] evaluated multiple parameters of mandibular morphology based on HFM patients' cephalometric radiographs; Elnaghy et al's[9] found the difference between mandibular ramus bone mineral density on the affected and nonaffected side of HFM patients by cone beam computerized tomography assessments; Chen et al's[10] investigated the cranial base involvements in HFM patients by 3-dimensional analysis, and Peng et al's[11] characterized airway changes in HFM adolescents.

Whereas an essential component of the mandible, the medullary cavity has never been covered in any report. Current quantification of bone marrow is mainly designed for marrow adipose tissue and relied on the contrast intensity of computed tomography (CT) or magnetic resonance imaging slices,[12] with low potential to analyze marrow cavity integratedly.[13] Our team ambitions at establishing a novel method to intravitally measure the volume of mandible medullary cavity in a 3-dimensional environment and probing into the difference between medullary cavity volumes on the affected and nonaffected side.

MATERIALS AND METHODS

This cross-sectional study collected information from patients with unilateral HFM diagnosis in the Plastic and Reconstructive Surgery Department of Shanghai Ninth People's Hospital from November 2014 to December 2020 for mandibular distraction osteogenesis. Patients must have preoperative full-craniofacial 3-dimensional CT scanning data in DICOM (Digital Imaging and Communications in Medicine) format to be included. The exclusion criteria were other craniofacial diseases and history of trauma or surgery to the mandible. Either the patients' parents or adult patients themselves had given written informed consent.

A 3-dimensional CT scanning was carried out by a 64-slice Somatom Definition Flash 80 kV CT scanner (Siemens). DICOM formatted data were then processed in Mimics Medical 21.0 (Materialise N.V., Leuven, Belgium). A 3-dimensional model of the mandible could be reconstructed (Fig. 1) and divided into affected and nonaffected sides along the plane defined by anatomical landmarks menton, pogonion, and point B as illustrated in Figure 2 by mask tools. After rendering, reconstructed models of both sides in binary STL format were imported into Geomagic Wrap 2017 (3D Systems Inc., North Carolina, USA). In this software, the medullary cavity could be isolated from the mandible model. The volumes (mm^3) of mandible entity, parts along with its medullary cavity could then be calculated by volume computing tool (examples shown in Figs. 3, 4). The ratio of medullary cavity volume to mandible volume on each side was also calculated to determine the proportion of the marrow in the bone.

Acquired variables including volume, volume ratio, age, gender, affected laterality, and Pruzansky-Kaban classification types were further performed in IBM SPSS Statics Software Package, Version 20.0 (IBM Corporation, New York, USA). Statistical methods include paired samples t test for comparison between volumes and their ratios on different sides, independent t test for comparison between volumes and ratios in different genders, 1-way analysis of variance for comparation of volume ratios throughout all Pruzansky-Kaban types, Pearson correlation analysis for relating age with volume ratios, and Spearman rank correlation analysis for relating nonparametric attributes with volume ratios. All statistical analyses in this study set $\alpha = 0.05$ and a significant $P < 0.05$.

RESULTS

A total number of 153 patients met the inclusion criteria, whose records were retrieved at the end of all treatments from the electronic medical archive. All patients were of Chinese Han ancestry with their age range between 3 months and 22 years. The mean age was 5.03 years with an SD of 4.16. Other epidemiological variables were listed in Supplemental Table 1 (Supplemental Digital Content 1, http://links.lww.com/SCS/E221).

Volumes presented in mean ± SD and relevant P values were concluded in Supplemental Table 2 (Supplemental Digital

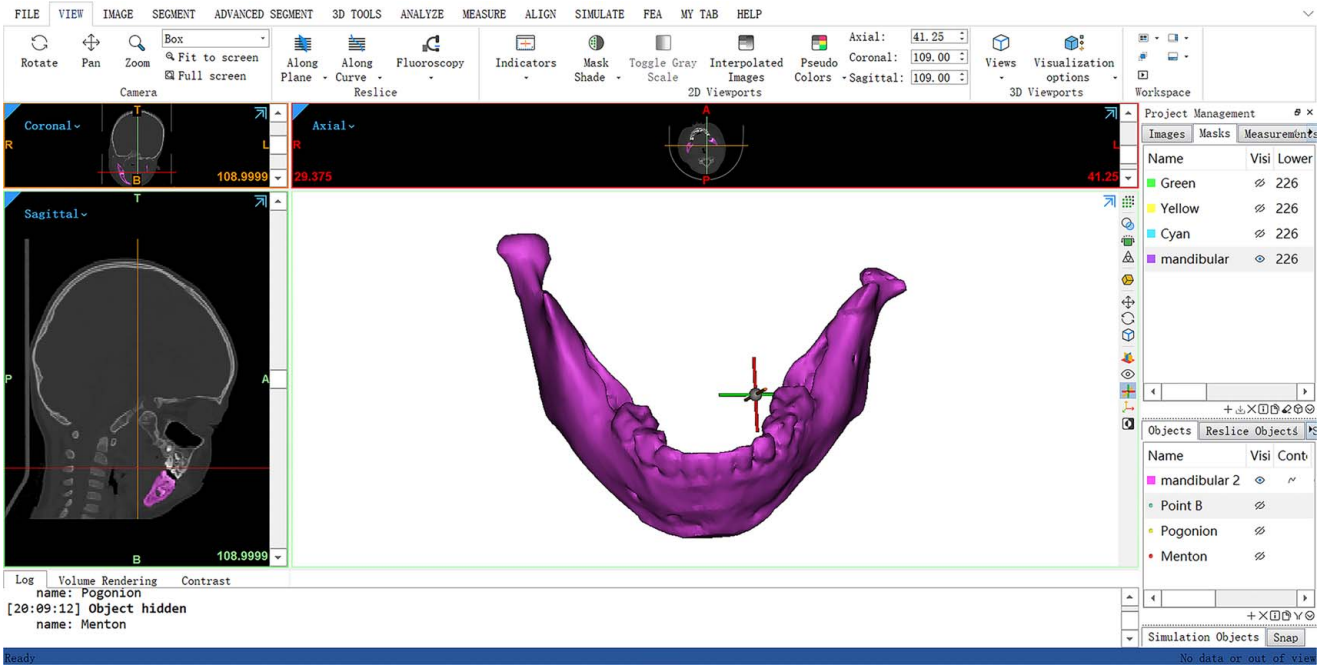

FIGURE 1. Representative image that shows 3-dimensional reconstruction of a mandibular model in Mimics 21.0.

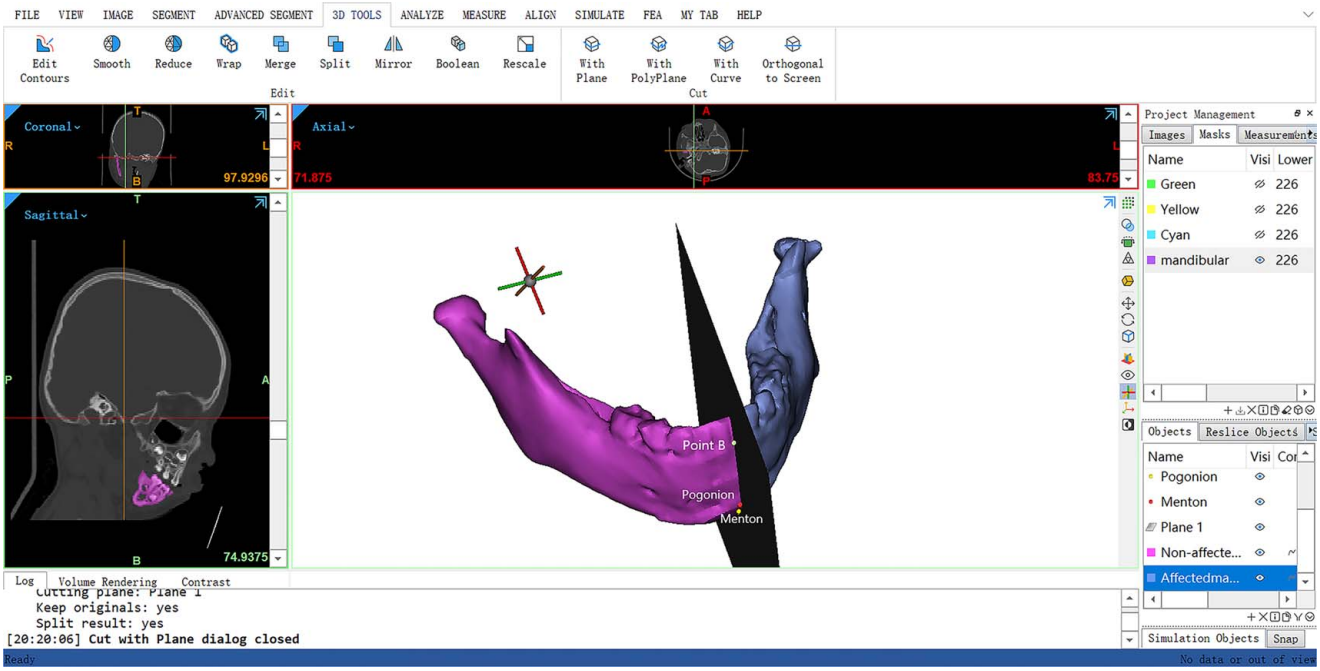

FIGURE 2. Representative image that shows a mandibular model cut into the affected and nonaffected side with the plane defined by point B, Pogonion and Menton. Point B, the deepest point of mandibular alveolar concavity. Pogonion, the most anterior point of mental symphysis. Menton, the most inferior and anterior point on mental region.

Content 1, http://links.lww.com/SCS/E221). Volumes of the entire mandible ($P = 0.012$), nonaffected side mandible ($P = 0.02$), and affected side mandible ($P = 0.008$) were significantly distinct in different genders. However, this discrepancy was not found in volumes of the entire medullary cavity, affected side medullary cavity, or nonaffected side medullary cavity. Nor was there any difference between volumes in various Pruzansky-Kaban types.

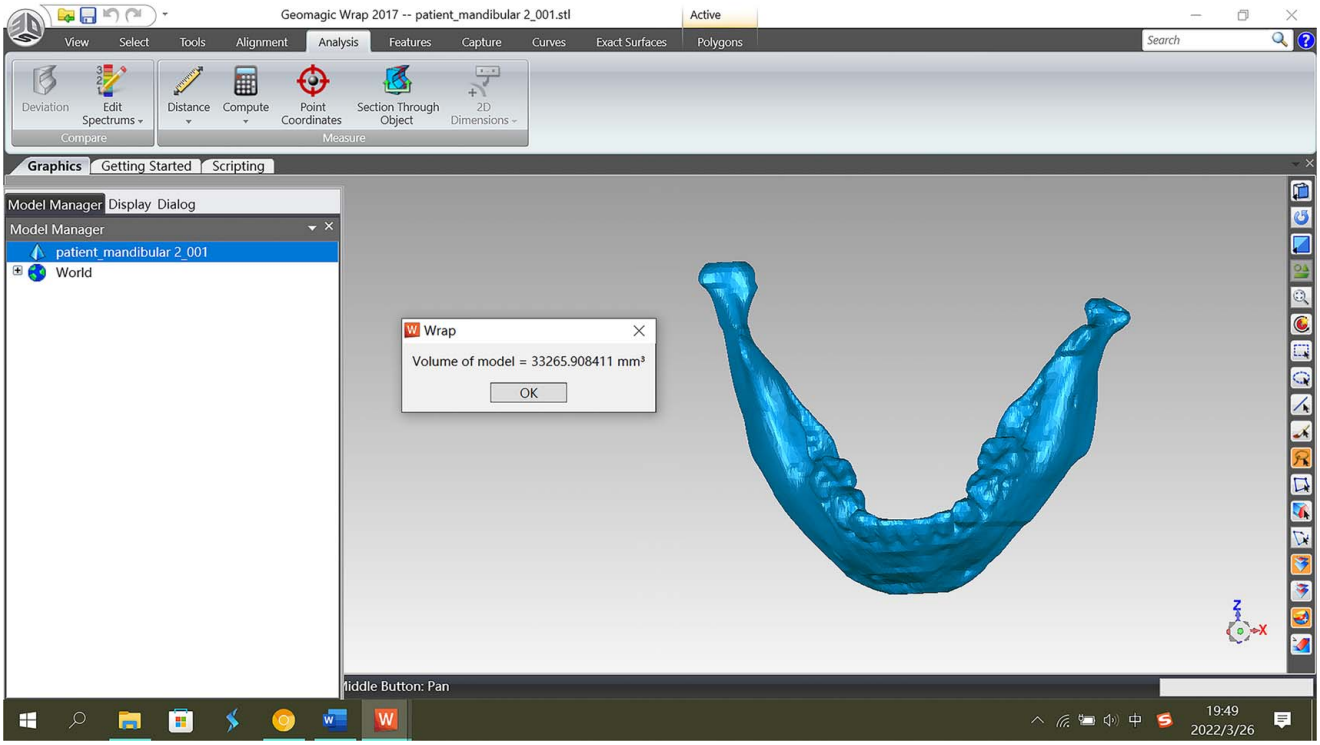

FIGURE 3. Representative image showing the measurement of entire mandibular volume in Geomagic Wrap 2017.

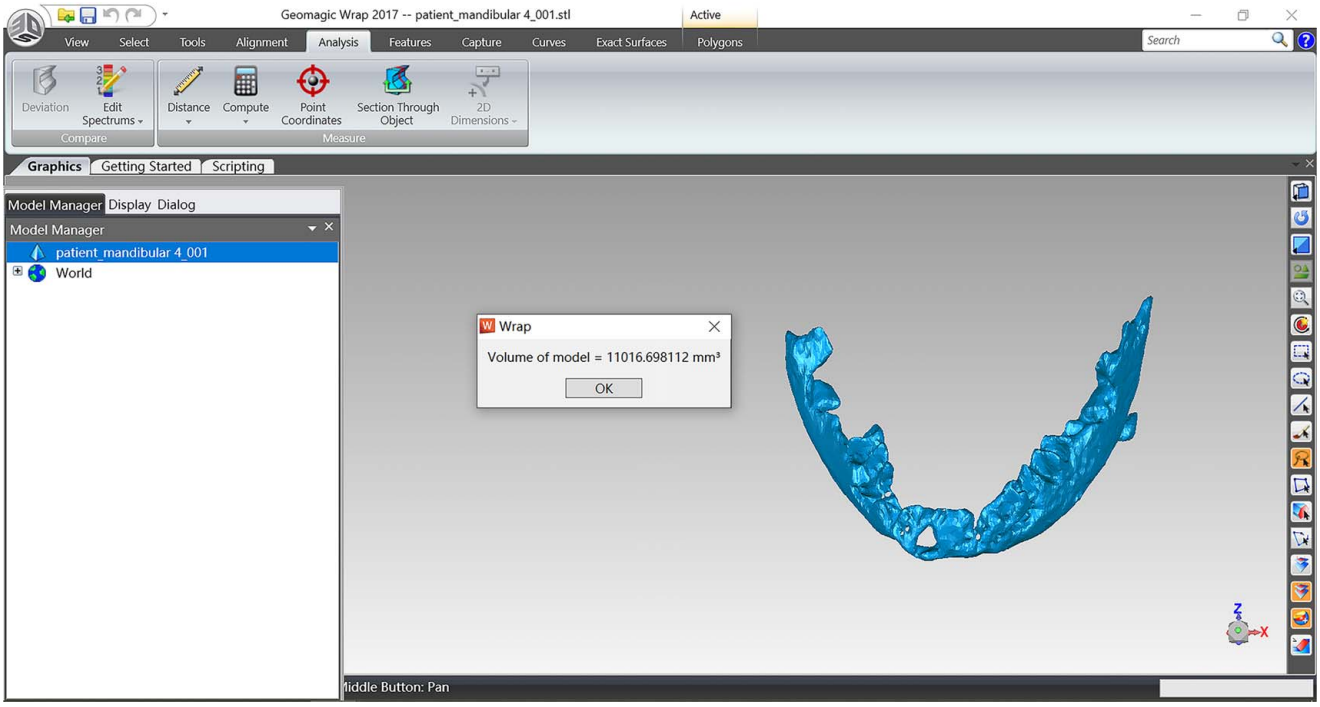

FIGURE 4. Representative image showing the measurement of entire medullary volume in Geomagic Wrap 2017.

Statistical significance was then found in mandible volumes ($P < 0.001$) and medullary cavity volumes ($P < 0.001$) on different sides. Correlation analyses showed that medullary cavity volumes were significantly related to mandible volumes on both the nonaffected and the affected side (both $P < 0.001$) with an r value of 0.569 and 0.514, respectively. The entire medullary cavity was also proportional to the entire mandible with a higher r value of 0.608 and $P < 0.001$. Moreover, volumes of the entire medullary cavity were in correlation with patients' age. The r value was 0.200 and P value was 0.013. Medullary cavity volumes on the nonaffected and affected side were both in correlation with age but in different degrees ($r = 0.214$, $P = 0.008$ versus $r = 0.170$, $P = 0.036$).

The ratios of medullary cavity volume the mandible on the nonaffected side (mean 5.60%, SD 5.44%) were significantly different ($P < 0.001$) from those of the affected side (mean 4.50%, SD 4.94%). Volume ratios of the nonaffected side did not differ among genders ($P = 0.409$) or Pruzansky-Kaban types ($P = 0.101$), nor did those of the affected side ($P = 0.146$ and 0.172, respectively). The volume ratio on the nonaffected side correlated to age while this correlation did not exist on the affected side ($r = 0.195$, $P = 0.016$ versus $r = 0.129$, $P = 0.112$). There was no correlation between Pruzansky-Kaban types and volume ratios on either side. For the nonaffected side $r = -0.098$, $P = 0.229$ and for the affected side $r = -0.015$, $P = 0.857$.

DISCUSSION

The emphasis of this study was laid on an unprecedented investigation into the volume of HFM patients' affected side mandibular medullary cavity. Our finding was a prominent smaller medullary cavity on the affected side. However, taken into consideration that there is an existential discrepancy in mandibular volumes on each side, and a correlation between mandibular volume and medullary cavity volume, ratios of the 2 volumes standing for the proportion of medullary in the mandible skeleton were adopted in analyses to rule out this interference.

The bone marrow is a complex organ composed of multiple cell lines with both hematopoietic and osteogenic functions based on which it could be divided into 2 systems: a hematological one and a stromal one. Hence, a smaller medullary cavity would lead to a reduced amount of bone marrow cells. The marrow's osteogenic potential derives from its stromal stem cells that could spontaneously differentiate into osteocytes even in vitro with no inducers. Stromal stem cells serve more than this as pluripotent stem cells with differentiation direction of various progenitor cells, fibroblasts, and reticular cells. There was no previous evidence on the connection between marrow sizes and skeletal developments, yet there has been proof in bone marrow transplantation researches of marrow cell quantity's direct influence on the marrow's osteogenic capability.[14] A larger mass of bone marrow transplanted induced more new bone formation.[15] Vice versa, limited bone marrow mass in the affected medullary cavity is a possible culprit to abnormal bone formation in the affected side of mandible.

This fault could be aggravated by reduced population of hematopoietic cells with consequent impairment on blood supply. Insufficiency blood supply could impede bone modeling and regeneration. Red bone marrow acts as the main component in the medullary cavity during infant and childhood. Free cells in the reticular structure of red marrow, namely blood cells of different stages, macrophages, adipocytes, and plasmacytes constitute the hematopoietic inductive microenvironment along with blood sinuses, nerves, and stromata. Only in a normally functional microenvironment could differentiation, proliferation, and developments occur. Any impact a shrunken red marrow would generate on the medullary microenvironment could bring about hematopoietic dysfunction.

After 12 weeks gestational age, cartilage in fetal bones decreases while bone formation and red marrow increases. The

weight of bone marrow is about 65 g in neonates, 90 g at 4 months and soars rapidly at 7 to 8 years old, in proportion to body weight gain to meet children's strong demand of growth. Although the weight of mandibular marrow cannot be measured intravitally, our result demonstrated that in HFM patients only on the nonaffected side, significant correlations of both medullary cavity volume and proportion with age was observed. On the affected side, the proportion of marrow in bone was irrelevant to patients' age and volumes of the medullary cavity correlated to ages on a lower scale and reliability, which signify a poorer potential of expansion. This may explain a higher reluctancy of growth in affected mandibular sides.[16]

Mandibular medullary cavity volumes were not in correlation to HFM classification; therefore, we cannot update a new phenotype marker for disease severity or develop new classifications. Despite this, the physiological nature of bone marrow decides that our discovery of abnormal medullary volume contributes towards further elucidating how clinical manifestations associate with HFM pathogenesis. Nonetheless some shortcomings hinder us from more concrete conclusions: the method of volume measurement was not validated; speculations about microenvironment changes needed to be verified by histological sections or cytometry; and an extra in vivo study to observe if mandibular growth or morphology could be impacted in murine models with partly occluded medullary cavity. Our curiosity about why HFM patients bear smaller medullary cavity and the causality between medullary volume and mandibular volume is yet to be resolved by further studies.

In addition, our effort to reconstruct and measure medullary cavity could facilitate with optimizing precise surgical designs. Reconstructive technology allows preoperative confirmation of inferior alveolar nerve canal shape and spatial position, which provides surgeons with a clear knowledge of covert structures in the mandible. Combined with augmented reality techniques, medullary cavity model will push customized surgery to a new high.

CONCLUSION

We probed into the volume of mandibular medullary cavity in HFM patients. Mandibular medullary cavities on the affected side were found to be smaller, of lower proportion in the mandible and with poorer potential of growth than that on the nonaffected side. This discrepancy was a possible culprit to uneven bone formation and blood supply on each side and might impact the medullary microenvironment. Our findings may foster knowledge towards an underlying link between HFM manifestation and pathogenesis.

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