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Three-dimensional evaluation of facial asymmetry in patients with hemifacial microsomia using stereophotogrammetry

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ABSTRACT

Purpose: To quantify the surface facial asymmetry in a group of young patients with hemifacial microsomia (HFM) and to investigate differences with a homogeneous sample of healthy subjects, using a novel stereophotogrammetric method.
Materials and methods: Twelve patients (mean age 13.1 ± 3.1 years) with different degrees of HFM and 15 healthy controls (mean age 12.2 ± 3.5 years) were imaged with a stereophotogrammetric facial scanner. The root mean square error (RMSE) of the distances between the corresponding points of each original photograph and its mirror copy was calculated for the whole face and for each trigeminal third, as defined by the innervation of trigeminal branches. A statistical analysis was performed to compare the RMSE value of all facial areas within each group and between patients and controls.
Results: RMSE values progressively increased from the upper to the lower third of face, both in patients and controls. The level of asymmetry was significantly higher in HFM subjects for middle third ($p < 0.01$), lower third ($p < 0.001$) and whole face ($p < 0.001$); no statistically significant differences were found between the groups for the upper third.
Conclusions: The reported technique provides an accurate topographic analysis of the facial asymmetry, and is recommended for conditions such as HFM affecting only part of the face.

1. Introduction

Hemifacial microsomia (HFM) is a congenital craniofacial malformation caused by asymmetrical hypoplasia of anatomical structures deriving from the first and second pharyngeal arches. This developmental abnormality variably involves the facial skeleton (mandible, maxilla, zygoma, and/or temporal bone), ear, cranial nerves and soft tissues, thereby creating a wide spectrum of phenotypic alterations.

HFM is the second most common craniofacial birth defect after cleft lip and palate, affecting 1 in 3000 to 1 in 5000 live births (Grabb, 1965).

Despite the heterogeneous pattern of HFM presentation, facial asymmetry is the most frequent feature, mainly due to unilateral soft tissue deficiency and mandibular hypoplasia (Cousley and Calvert, 1997).

Patients with HFM need prolonged, multidisciplinary team care, which depends on the degree of deformity of the facial structures, and it includes repair of bony asymmetry as well as soft tissue defects and auricular anomalies (Brandstetter and Patel, 2016).

Three-dimensional (3D) evaluation of facial morphology is advisable for the management of HFM. The quantification of asymmetry can be useful to support the diagnostic process and treatment planning. Moreover it can be performed during follow-up examinations for growth monitoring and for evaluating immediate and long-term treatment outcomes. Thus, an objective, non-invasive technique to calculate facial asymmetry is recommended.

Recently, several studies reported the assessment of facial topography using non-invasive methods, such as laser surface scanners (Yu et al., 2009; Primozic et al., 2012; Djordjevic et al., 2014), stereophotogrammetry (Plooij et al., 2009; Verhoeven et al., 2013; Othman et al., 2014; Baysal et al., 2016), or

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ultrasonographic measurements (Di Blasio et al., 2017). Particularly, 3D stereophotogrammetry has been extensively investigated for the evaluation of soft tissue surface facial asymmetry in healthy subjects (Berssenbrügge et al., 2014; Taylor et al., 2014; Alqattan et al., 2015; Kornreich et al., 2016; Ozsoy, 2016; Verhoeven et al., 2016), asymmetric patients (Patel et al., 2015; Codari et al., 2017) or artificially created asymmetric faces (Verhoeven et al., 2016; Zaidel and Deblieck, 2007).

To perform facial analysis on 3D photographs, two different approaches have been described: landmark- and surface-based methods. The first procedure consists of placing a variable number of landmarks on the 3D image and measuring distances either between landmarks and the facial symmetry plane (Alqattan et al., 2015) or between landmarks and their mirror-corresponding copies (Verhoeven et al., 2016). On the contrary, the surface-based method, which is landmark-independent, takes into account all available facial points, making a superimposition between the whole original surface image and its mirror copy. Automated matching is performed by using a surface registration algorithm, the Iterative Closest Point Algorithm (ICP), which searches for the closest point-to-point relationship between the two surfaces and calculates their average distance (Besl and McKay, 1992).

Surface assessments have already been found to be more sensitive and comprehensive than landmark measurements, allowing a full face analysis (Verhoeven et al., 2016); however a local evaluation focused on selected facial regions might be advocated for specific pathologies, such as HFM, affecting only part of the face.

The present study aims to quantify surface facial asymmetry in a group of young HFM patients with various phenotypes, and to investigate differences between a homogeneous sample of healthy subjects, using a novel stereophotogrammetric method of 3D assessment. Such a method has been recently described and it combines surface- and landmark-based approaches, considering the whole face and the different facial thirds, as defined on the territories of trigeminal distribution (Codari et al., 2017).

2. Materials and methods

2.1. Sample

Twenty-seven Caucasian subjects were recruited. The sample consisted of 15 healthy subjects (9 females; 6 males; mean age 12.2 ± 3.5 years) and 12 HFM patients (7 females; 5 males; mean age 13.1 ± 3.1 years) treated at the Orthodontic Section of the Academic Hospital of Parma, Italy. Based on the severity of anatomical anomalies, HFM patients were classified according to the system proposed by Kaban (Murray et al., 1984) (Table 1): type I (2 patients), type IIA (3 patients) and type IIB (4 patients). Three patients were diagnosed as affected by Goldenhar syndrome. None of the included subjects were surgically treated.

Inclusion criteria for control group were no history of facial trauma, maxillofacial surgery, craniofacial syndromes or deformities.

The principles outlined in the Declaration of Helsinki were followed throughout the present study. In all cases, informed consent was obtained from the parents or legal guardians of the patients. The research has been performed in accordance with the Ethical Guidelines as provided by the Institutional Review Board (IRB) of the University of Parma.

2.2. Stereophotogrammetric system and image acquisition

Images from all subjects were acquired by using Face Shape 3D Maxi Line Photogrammetric Scanner manufactured by Polishape 3D Srl (Bari, Italy). The scanner incorporated six reflex digital cameras (Canon EOS 1100D, of 12,2 megapixels, 3–6 frames for seconds) mounted on a rigid rectangular support with the following angulations: two cameras were arranged in the central position and two cameras on each side of the subject. Participants were seated on an adjustable chair and were asked to adopt a neutral facial expression, keeping their jaws in a relaxed state. Natural head posture was adopted, as it has been shown to be clinically reproducible (Cassi et al., 2016). Subjects were also recommended to look at a specific point marked on the opposing wall. After the acquisition process, a 3D elaboration was performed, using the software View box. The final 3D output was a triangulated polygon mesh.

2.3. Asymmetry quantification

Facial symmetry was quantified through the mirroring approach. The 3D image contour was manually refined, deleting peripheral areas along the forehead, cheeks and mandibular-neck angle outlines. The hairline, ears and neck and shoulders portions were removed because they are vulnerable to errors and can affect asymmetry quantification (Maal et al., 2008); thus, only craniofacial structures of interest for maxillofacial morphometric analysis were taken into account.

To improve the operator precision in selecting the different facial areas, 16 anthropometric landmarks (seven bilateral and two medial) were manually marked on the digital facial surface following a pre-customized template. Their coordinates on the x, y, and z planes were collected from the software and recorded in an Excel spreadsheet.

The original image was duplicated in a mirror version by reflecting along an arbitrary plane outside of the face, in accordance with other authors (Cevidanes et al., 2011). Subsequently, the original and mirrored images were fixed into identical spatial coordinates and matched with respect to surface of the forehead area. Such an area was previously selected by tracing a horizontal line tangent to the Nasion point. Superimposition procedure was performed using an automatic View Box function called “Auto Registration” and based on the ICP algorithm for the best-fit registration.

The original facial surface was further divided into an upper third (UT), middle third (MT), and lower third (LT), according to the territories of distribution of trigeminal branches. Thus, each facial third was defined using an appropriate “area selection” tool, which allowed the operator to manually connect the anatomical landmarks.

Finally, the root mean square error (RMSE) was calculated on the whole face, on the forehead area and on each trigeminal third. This variable averages the distances between the original and the reflected surfaces, and it is considered a reproducible and accurate way to measure facial asymmetry (Taylor et al., 2014).

Table 1
Kaban classification of HFM, which distinguishes 5 categories according to the severity of the anatomical anomalies.

Type I	Hypoplastic temporomandibular joint
Type IIa	Hypoplastic and abnormal shape of mandibular ramus, condyle and temporomandibular joint
Type IIb	Mandibular ramus is hypoplastic and markedly abnormal in form and location, being medial and anterior
Type III	Absence of mandibular ramus
Type IV	Mandibular body hypoplasia

Deviations between the original and mirror facial images were also presented graphically as colour maps and quantitatively on histograms.

The adopted method is presented step-by-step in Fig. 1.

2.4. Statistical analysis

Statistical analyses were performed using IBM-SPSS version 22 and the open source statistical system R, version 3.4.2.

Descriptive analysis has included the main position, dispersion and shape indexes, such as mean, median, mode, 5% trimmed mean, variance, standard deviation, interquartile difference, minimum, maximum, range, asymmetry coefficient and kurtosis. Standard errors and 95% confidence intervals were also reported.

The Chi-square test was used to check differences in sex distribution between control and patient groups, while the Student t test was used to check age difference.

To investigate the intra-observer reliability, the 3D images of 11 randomly selected subjects were analysed after a 2-week interval; facial landmarks were digitally marked and topographic areas were manually selected.

The repeatability in landmarks digitizing process was tested using the Pearson correlation coefficient (r) and Lin concordance coefficient (rho.c). Each landmark is described by three spatial coordinates (x,y,z), which were analysed in couple by statistical tests. Couples of coordinates have an excellent reproducibility if "rho.c" and "r" are greater than 0.9, good if greater than 0.8, not optimal, however acceptable if greater than 0.7. The reliability coefficients indicate coherence between two separate measurements of corresponding landmarks. For both intra-observer comparisons the Pearson correlation coefficient and Lin concordance coefficient were used to calculate the reliability coefficients between the first and second measurements of a landmark.

To investigate the repeatability in surface area selection, the RMSE values of each facial area were calculated a second time and intraclass correlation coefficients (ICC) were estimated.

Descriptive plots were used for representing RMSE values of investigated facial areas in the two groups. Normality distribution of the data was tested using the Kolmogorov–Smirnov test and Shapiro–Wilk test.

Two way mixed-design analysis of variance (ANOVA) with Tukey *post hoc* tests were used to compare the RMSE value of all facial areas within each group and between controls and patients. Results were considered statistically significant for a p-value less than 5% ($p < 0.05$).

3. Results

In this study, 15 control subjects and 12 patients affected by HFM were evaluated. No statistically significant differences were found in age ($p = 0.1$, Student t test) and sex distribution ($p = 0.9$, Chi-square test).

The statistical analysis of the repeated landmarks digitizing showed levels of reproducibility ranging from "excellent" to "good." The highest level of concordance and correlation ($r = 1$) was found for the Columella – z coordinate couple, while the lowest value was $r = 0.74$ for the Alar right – y coordinate couple.

With regard to the repeatability in surface area selection, the ICCs resulted high (between 0.968 and 0.999) for all RMSE measures (Table 2).

Values of RMSE in control subjects and patients, divided for each facial area, are presented in Fig. 2. Overall, patients had a larger asymmetry in all facial thirds than control subjects; the difference appears particularly evident for the middle and lower thirds.

Two-way mixed-model ANOVA showed a statistically significant difference in RMSE values between control subjects and patients with regard to middle third ($p < 0.01$), lower third ($p < 0.001$) and whole face ($p < 0.001$); no statistically significant differences were found between the groups for upper third and forehead (Table 3).

Post hoc analysis showed that among control subjects there was no significant difference between forehead and upper thirds and between upper third and middle third ($p > 0.05$); on the other hand, there was a significant difference for the following comparison: forehead versus middle third ($p = 0.01$), forehead versus lower third ($p < 0.001$), upper third versus lower third ($p < 0.001$) and middle third versus lower third ($p < 0.001$).

Comparing the different thirds within the patient group, statistically significant differences were found in all cases (Table 4).

4. Discussion

In the present study surface facial asymmetry was assessed in a sample of growing subjects with hemifacial microsomia compared to a healthy control group. We propose a combined method, both surface- and landmarks-based, which measures the distance between the original and the mirror 3D images. RMSE was chosen as reference variable, being already adopted by several authors as a single numeric value quantifying facial surface symmetry (Maal et al., 2011; Taylor et al., 2014; Patel et al., 2015). Moreover, colour maps were also elaborated for each patient, giving a graphical representation of the distance differences between the two superimposed 3D images. Colour maps were completed by histograms containing qualitative and quantitative information, with a colour-coded scale that might be customized by specifying the distance range. Such a digital tool should be considered useful for diagnostic imaging and visual examination of the asymmetry.

To the best of our knowledge, no study has been published so far performing quantitative facial measurements on a large sample of HFM patients. Recently, Taylor et al. calculated the RMSE value between the native and reflected faces of a single patient with mild HFM and compared it with normative data of 100 healthy volunteers (Taylor et al., 2014). In a case reported by Jayaratne et al., the authors describe the applications of 3D photogrammetry for surgical planning and follow-up assessment of the volumetric changes in a 19-year old woman affected by HFM (Jayaratne et al., 2010a). The same authors in another paper showed the colour map generated from the superimposition of pre-surgical and post-surgical 3D photos of a HFM case (Jayaratne et al., 2010b). Yu et al. investigated a method to evaluate the facial asymmetry using 3D laser surface scanning images, including three HFM patients in the study sample (Yu et al., 2009); however, the investigation was focused on a questionnaire administered to patients and surgeon regarding the desired therapy outcomes as simulated in computers by a flip-registration procedure. The objective assessment of facial asymmetry in HFM subjects was not reported.

With regard to the registration process, the surface matching between the native and the mirror images was performed by selecting the forehead area as superimposition region. This area represents the less asymmetric and most stable part of the face, being slightly affected by growth. Thus, also because the relatively thin and immobile nature of the overlying soft tissue, the area is considered the ideal reference region to achieve the best alignment during the superimposition procedure (Miller et al., 2007; Jayaratne et al., 2010b).

The main aspect of our method consists in the topographic analysis of facial morphology, which includes a global and a local evaluation of surface discrepancy. Such an approach is not new: other authors provided a local subdivision of the face, most of them dividing the facial areas into horizontal thirds (Meyer-Marcotty

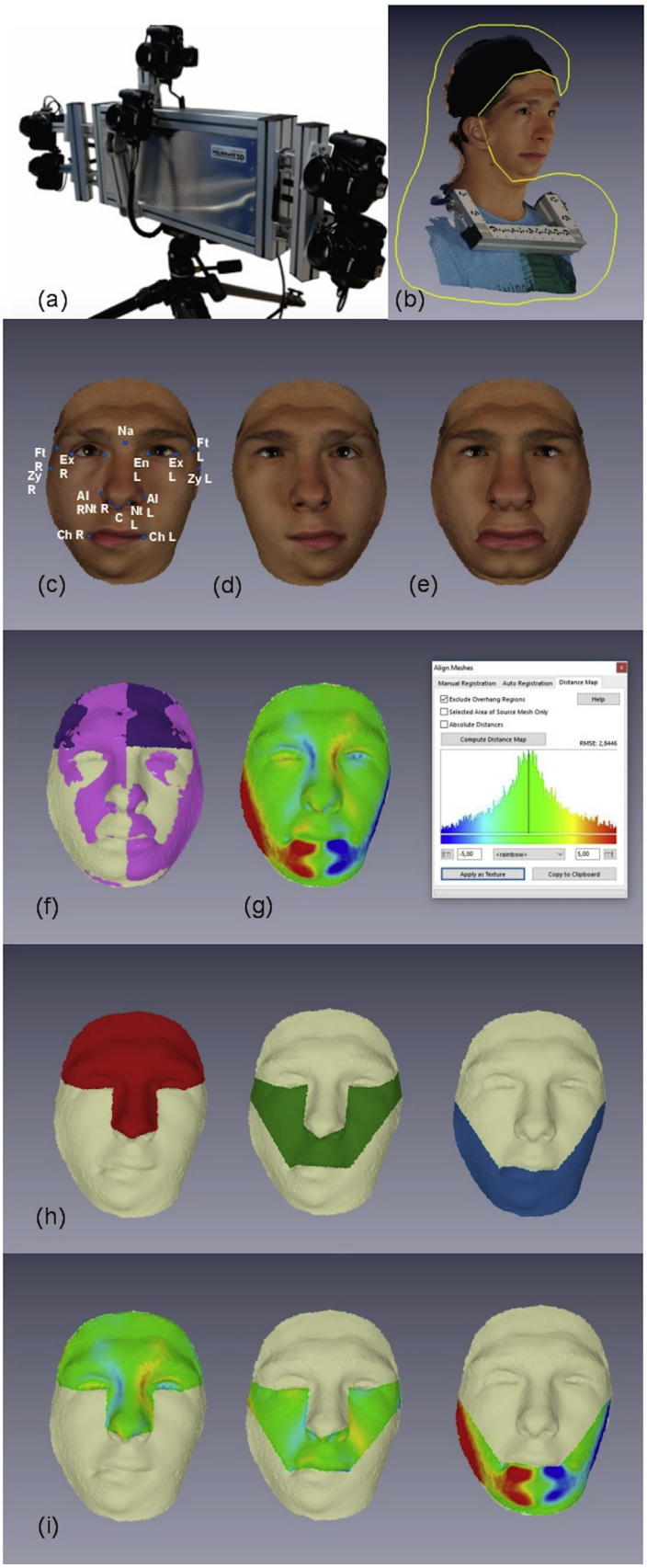

Fig. 1. Flowchart illustrating the proposed method for facial asymmetry analysis. a) Capture of a 3D facial surface scan image. b) Exclusion of confounding areas. c) Selection of the following facial landmarks: Zygion right (Zy R); Zygion left (Zy L); Frontotemporale right (Ft R); Frontotemporale left (Ft L); Nasion (Na); Exocanthion right (Ex R); Exocanthion left (Ex L); Endocanthion right (En R); Endocanthion left (En L); Cheilon right (Ch R); Cheilon left (Ch L); Alare right (Al R); Alare left (Al L); Nostril top point right (Nt R); Nostril top point

et al., 2011; Primozic et al., 2012; Djordjevic et al., 2014; Patel et al., 2015) or into more regions (Alqattan et al., 2015; Kuijpers et al., 2015; Ozsoy, 2016; Verhoeven et al., 2016). We followed the method recently described by Codari, which divides the face into thirds, based on trigeminal branches distribution territories for somatic sensitivity (Codari et al., 2017). The trigeminal area selection corresponds to different embryological origins and it is considered a functional subdivision of the face, thus being more appropriate for the morphometric analysis of a congenital malformation such as HFM. In fact, the middle and the lower thirds are usually delimited by a horizontal axis tangent to the subnasal landmark, splitting the maxillary bone into two parts; on the contrary, the trigeminal area selection maintains the anatomical and functional integrity of the facial structures. Additionally, the manual selection seems to be sufficiently precise, as the areas considered are more easily recognized.

Our method differs from that previously described in regard to some important features. Codari et al. divided the original image in two hemi-surfaces, which were subsequently subdivided into three different facial thirds; by contrast, we avoided a delimitation on the mid-sagittal plane, performing the trigeminal subdivision only horizontally and combining the two hemifacial sides. We could therefore reduce the amount of anthropometric landmarks to be selected. Moreover, since structures located on the facial midline as nose, philtrum and chin are often displaced by the asymmetry, the individuation of a mid-sagittal plane can be misleading and may affect the precision of measurements (Meyer-Marcotty et al., 2011). Based on the same considerations, the mirror image was obtained by flipping the original one along an arbitrary plane instead of the mid-sagittal plane, in accordance with other authors (Nkenke et al., 2003, 2006; Yu et al., 2009). Our method is therefore independent by any symmetry plane and it is not influenced by the size of the face.

Another possible advantage of our procedure regards the positioning of anthropometric landmarks: we manually selected the soft tissue points on the 3D images using a mouse-driven cursor instead of marking them on the patient's skin before the acquisition. Performing landmark selection directly on a patient is time consuming, even though it is considered more precise, especially for points whose identification requires both visual inspection and palpation.

Landmarks with well-defined borders or edges, such as those near orbits (endocanthion and exocanthion) and mouth (cheilion) are easier to determine visually than the ones located on convex surfaces, which require palpation. Landmarks used in this study showed good intraexaminer consistency. However, it is remarkable that landmark selection was performed to delimit area selection and not to measure distances between points. Importantly, the repeatability of surface area selection resulted high, thus proving the effectiveness of combining a surface- and landmark-based approach.

Despite the high reproducibility of the method presented here, the learning curve of the software requires a quite prolonged and specific training program.

The descriptive plot shows that the RMSE values progressively increase from the upper to the lower third of the face, both in patients and controls. Particularly, there is statistically significant difference in the amount of asymmetry between each facial third within the patients group; instead, among control subjects, the lower third is significantly more asymmetric compared to the middle and upper thirds.

Table 2
Values of intraclass correlation coefficient (ICC) for repeated RMSE measurements.

first and second measurements	ICC (95% confidence interval)	p value
Forehead	0.999 (0.999; 1)	0.0001
Upper third	0.990 (0.964; 0.997)	0.0001
Middle third	0.983 (0.937; 0.995)	0.0001
Lower third	0.993 (0.974; 0.998)	0.0001
Whole face	0.994 (0.979; 0.998)	0.0001

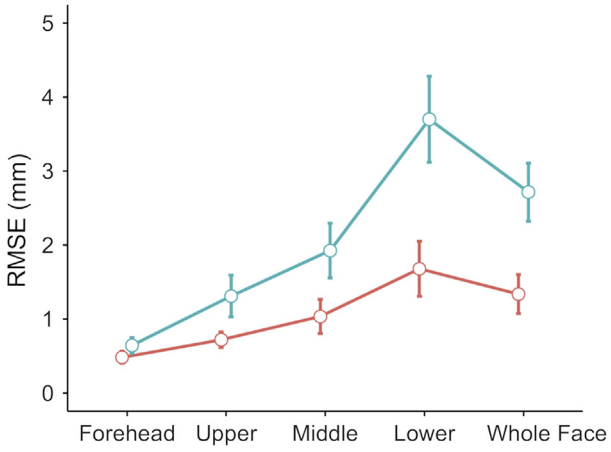

Fig. 2. Descriptive plots representing root mean square error (RMSE) values (mean and 95% confidence interval) of controls subjects (red) and patients (blue) for the following facial region: forehead, upper, middle, and lower thirds, whole face.

Table 3
Comparison of RMSE values of each facial area between patients and controls.

	Patients (n = 12)		Controls (n = 15)		Difference	p value
	Mean	SD	Mean	SD		
Forehead	0.64	0.18	0.48	0.16	0.16	0.999
Upper third	1.31	0.49	0.72	0.21	0.59	0.191
Middle third	1.93	0.65	1.03	0.46	0.90	0.004
Lower third	3.70	1.02	1.68	0.73	2.02	<0.001
Whole face	2.72	0.69	1.34	0.52	1.38	<0.001

Statistical comparison were performed with two-way analysis of variance ($p < 0.05$).

Table 4
Comparison of RMSE values between each facial area within patient and control groups.

	Patients	Controls
	p value	p value
Forehead versus upper third	0.003	0.83
Forehead versus middle third	<0.001	0.01
Forehead versus lower third	<0.001	<0.001
Upper third versus middle third	0.01	0.49
Upper third versus lower third	<0.001	<0.001
Middle third versus lower third	<0.001	<0.001

Statistical comparison were performed with Tukey post hoc test ($p < 0.05$).

left (Nt L); Columella (C). d) Creation of a mirrored image. e) Superimposition of the mirrored duplicate on the original image. f) Automatic matching of the original (cream) and mirror (pink) meshes, using the forehead area (purple) for the surface-based registration. g) Quantification of the asymmetry calculating RMSE value and elaboration of a colour-coded map to get a visual perception of the distance differences between original and mirrored facial areas. Colours key legend: colours at the right side of the histogram (red) depict outward regions that are in front of the reference surface; colours toward the left end of the scale (blue) represent inward regions that are behind the reference surface; colours corresponding to the middle of the scale (green) highlight regions that have minimal or no differences between the 2 superimposed surfaces. h) Bilateral delimitation of trigeminal thirds connecting manually the anthropometric landmarks. i) Calculation of RMSE of each facial area (upper, middle and lower third).

Our results are consistent with previous findings, reporting that the inferior portion of the face is more asymmetric, even in presence of a normal appearance (Ferrario et al., 1994; Haraguchi et al., 2008).

As expected, patients have significantly greater asymmetry of the whole face when compared to controls; however, if we consider the distribution of the asymmetry according to the distinct facial regions, the degree of asymmetry results significantly increased in the middle and the lower thirds. On the other hand, no statistical differences were found for the upper third and forehead area between HFM subjects and controls. As facial dysmorphology selectively affects maxillary and mandibular structures of HFM patients, the present findings confirm the accuracy of the proposed morphometric analysis in the localization of tissue discrepancy. Interestingly, despite the fact that the upper third is less asymmetric than the other two, it is still more asymmetrical in patients than in control subjects. Such a finding can be explained by taking into account that, according to the trigeminal division, the upper third includes the nose, which has been proved to play a crucial role on the perception of facial asymmetry and might be affected by the unbalanced facial development of HFM.

5. Conclusion

This study describes a three-dimensional, non-invasive and objective method for the accurate localisation and quantification of the surface facial asymmetry in subjects with hemifacail microsomia.

The procedure showed high reproducibility and accuracy on detecting morphometric differences between patients and controls; thus, it is applicable in the topographic analysis of syndromic and non-syndromic asymmetric pathologies.

The precise assessment of surface facial morphology with stereophotogrammetry is useful both for craniofacial research and for clinical practice, providing additional information for diagnosis, treatment planning and follow-up.

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Conflict of interest

The authors declare that they have no conflicts of interest.

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