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ORIGINAL ARTICLE

Mandibular Asymmetry in Patients With the Crouzon or Apert Syndrome

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The aim of this study was to describe directional and fluctuating mandibular asymmetry over time in children with Crouzon or Apert syndrome. Mandibular asymmetry of children between 7.5 and 14 years of age with Crouzon syndrome (n = 35) and Apert syndrome (n = 24) were compared with controls (n = 327). From panoramic radiographs, mandibular directional and fluctuating asymmetry was determined for the three groups. Multilevel statistical techniques were used to describe mandibular asymmetry changes over time. Patients with Crouzon and Apert syndromes showed statistically significant more fluctuating asymmetry for mandibular measures than did controls. Between the Crouzon and Apert syndromes groups, no statistical differences were found in directional and fluctuating asymmetry. The control group showed statistically significantly more directional asymmetry than did patients with Crouzon or Apert syndrome. The controls showed no change over time for the directional asymmetry of condylar-ramal height; however, the directional asymmetry of the gonial angle increased. Patients with Crouzon syndrome showed side dominance for only condylar-ramal height; whereas, patients with Apert syndrome did not show dominance for any of the measurements. Apert and Crouzon syndromes showed developmental instability, in contrast to the controls. No statistically significant longitudinal differences were found for either the directional or the fluctuating asymmetry between Crouzon and Apert syndromes. Findings for fluctuating and directional asymmetry for both syndromes may indicate an inability to cope with genetic and environmental stress during development and treatment, compared with untreated nonsyndromic individuals.

KEY WORDS: *Apert syndrome, Crouzon syndrome, directional asymmetry, fluctuating asymmetry, mandibular asymmetry*

Development of facial symmetry in children with premature closure of one or more craniofacial sutures (craniosynostosis) has not been well studied. Facial symmetry is most commonly associated with a state of facial equilibrium in which there is correspondence in size, shape, and arrangement of facial landmarks on both sides of the face (Peck et al., 1991). Many studies have demonstrated a certain asymmetry of structures as a natural, biologically occurring phenomenon (Woo, 1931; Thompson, 1943; Melnik, 1992). Asymmetry is measured as the left minus the right value of a structure. Some authors suggested that a difference of sides between 3% and 5% may be a normal population mean (Farkas and Cheung, 1981; Skvarilova, 1993). The point where normal asymmetry becomes abnormal cannot easily be defined because no standard outcome measurements for normal and abnormal asymmetry exist (Liukkonen et al., 2005; Kambylafkas et al., 2006). Asymmetry of bilateral structures can be distinguished in two different categories (Fig. 1; Table 1) (Van Valen, 1962). The first category includes two different types of asymmetry: directional asymmetry and antisymmetry. For directional asymmetry there is a systematic difference, with one side being consistently larger or more dominant than the other (Fig. 1a; Table 1) (Van Valen, 1962; Liukkonen et al., 2005). Most individuals are asymmetrical either to the left or right side (>95%). In contrast, antisymmetry occurs when the left-side and right-side individuals are almost equally present in a sample; the mean of the total population is centered around zero (Fig. 1b; Table 1) (Van Valen, 1962). Presumably, these two

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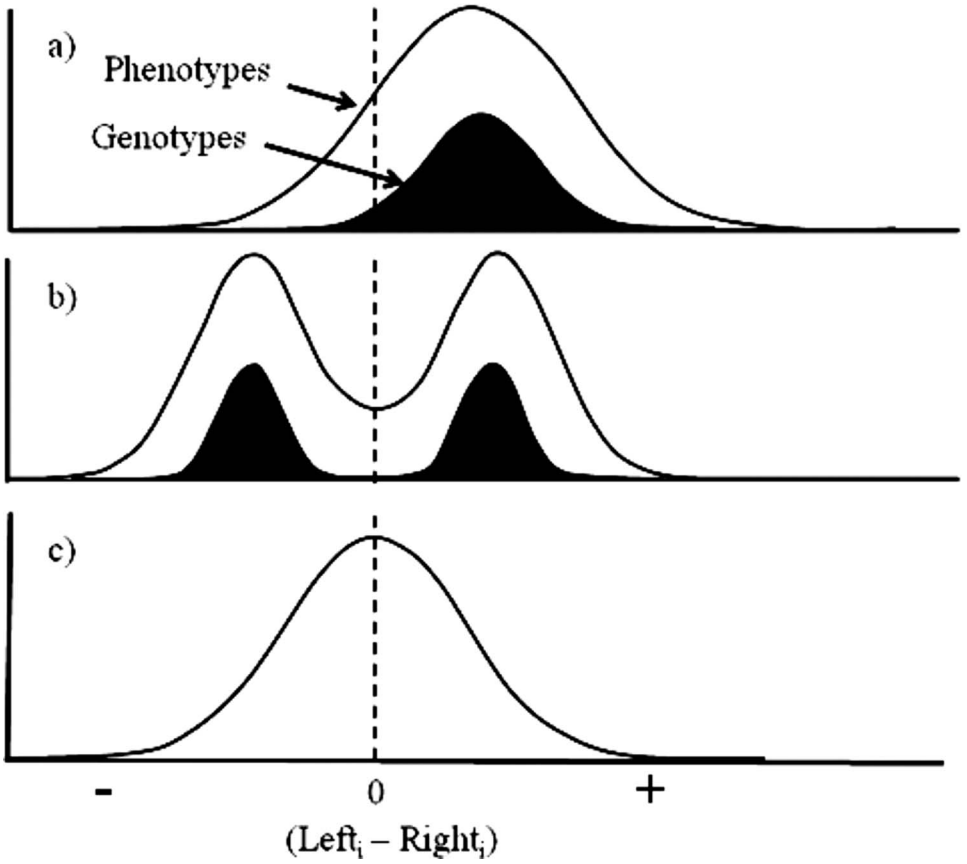

FIGURE 1 Three types of asymmetry. a: directional asymmetry; b: antisymmetry; c: fluctuating asymmetry (Palmer and Strobeck, 1986).

types of asymmetry produce growth discrepancies and have a genetic basis (Van Valen, 1962).

The second category of asymmetry, fluctuating asymmetry, can also occur (Fig. 1c; Table 1) (Van Valen, 1962). Fluctuating asymmetry refers to random deviations from perfect symmetry in bilateral structures and is frequently used as a measurement of developmental instability (Van Valen, 1962; Adams and Niswander, 1967; Swaddle, 2003; DeLeon and Richtsmeier, 2009). The degree of fluctuating asymmetry during growth may reflect developmental instability caused by stress (Van Valen, 1962; Adams and Niswander, 1967; Swaddle, 2003; DeLeon and Richtsmeier, 2009). The amount of stress experienced by individuals during growth may increase with physical impact or mental limitations (Van Valen, 1962; Adams and Niswander, 1967). Both directional and fluctuating asymmetry of craniofacial structures have been measured (Melnik, 1992; DeLeon and Richtsmeier, 2009).

During growth in normal children, both increases and decreases in directional asymmetry of the mandible have

TABLE 1 Definition and Distribution of Directional Asymmetry, Antisymmetry, and Fluctuating (L = Left Side, R = Right Side)

	Directional Asymmetry (DA)	*Antisymmetry (AS)*	*Fluctuating Asymmetry (FA)*
Definition	Directional asymmetry is characterized by a symmetry distribution that is not centered around zero but is biased significantly toward either the left or the right side. It is frequently used as a measurement of developmental precision and is caused primarily by genetic deviations (Fig. 1a)	Antisymmetry is a different, rare type of DA. It is characterized by being centered around a mean of zero. However, there is almost an equal distribution of left-side and right-side population in the same group (Fig. 1b)	Fluctuating asymmetry is characterized by small deviation from perfect symmetry in bilateral structures. It is frequently used as a measurement of developmental instability during the growth caused by minor environmental or genetic deviations (Fig. 1c)
Formula	$DA = (L - R)/[(L + R)/2]$	$AS = (L - R)/[(L + R)/2]$	$FA = (L - R)/[(L + R)/2]$
Distribution	The mean of left minus right side is zero, or a small deviation toward either left or right side in normal population	The mean of left minus right side is zero in normal population with nonnormal distribution (usually bimodal)	Fluctuating asymmetry is the absolute difference between the left and right side of a character. The differences of the right and left sides have a mean of zero with normal variation
Values	Positive or negative values possible	Positive or negative values possible	Only positive values possible

been observed (Melnik, 1992). Dominance of both the left and right sides of the mandible has been described (Vig and Hewitt, 1975; Peck et al., 1991). In normal children with developmental homeostatis, fluctuating asymmetry should be minimal (Fig. 1c; Table 1). Decreased fluctuating asymmetry indicates that development is relatively stable and unaffected by genetic or environmental distortions over time (Van Valen, 1962; Palmer and Strobeck, 1986; DeLeon and Richtsmeier, 2009). Developmental homeostasis can sometimes be distorted during growth by minor developmental problems, resulting in increased fluctuating asymmetry. Developmental instability during normal growth is small if sufficient homeostasis or buffering occurs (Palmer and Strobeck, 1986).

Craniosynostosis associated with the Crouzon syndrome (1 in 25,000 live births) and Apert syndrome (1 in 60,000 live births) results in severe craniofacial dysmorphology (Cohen and Kreiborg, 1992; Reardon et al., 1994; Kreiborg and Cohen, 1998). The craniosynostosis in these syndromes could indirectly influence mandibular development and create asymmetries (Costaras-Volarich and Pruzansky, 1984; Boutros et al., 2007). However, limited growth data are available from patients with the Crouzon or Apert syndrome due to the very low prevalence (Costaras-Volarich and Pruzansky, 1984; Kreiborg and Cohen, 1998). More information about asymmetry in patients with the Crouzon or Apert syndrome is needed in order to better understand how these patients react to possible environmental stress-related factors and genetic influences during growth. Therefore, the aim of this study was to evaluate and to describe the development of directional and fluctuating asymmetry over time in patients with Crouzon or Apert syndrome.

Materials and Methods

Sample Preparation and Radiographic Scans

Panoramic radiographic data of 72 white patients (age range, 3 to 33 years) with Crouzon syndrome (25 boys and 17 girls) or Apert syndrome (11 boys and 19 girls) were collected from the Craniofacial Center of the Erasmus Medical Center, Sophia Children's Hospital in Rotterdam, The Netherlands. The clinical diagnosis of the syndromes was genetically confirmed by mutations on the *FGFR2* or *FGFR3* genes (Table 2) (Wilkie et al., 1995; Mathijssen, 2000). From these data, only radiographs of patients between 7.5 and 14 years of age were selected in order to compare the same age range in nonsyndromic controls. The syndromic patients had undergone various surgical and orthodontic interventions prior to the observation period. The surgical interventions included, for example, intracranial expansion (sometimes life-saving surgeries) or surgical interventions at the hands or feet (Dutch Association Plastic Surgery, 2010). The panoramic radiographs were taken according to the Dutch team protocol (Dutch Association Plastic Surgery, 2010). From all the available panoramic radiographs, only the radiographs that were performed with sufficient diagnostic quality were used. The radiographs were taken before any mandibular surgery or mandibular distraction to prevent possible distortions of the mandibular measurements. At least two panoramic radiographs from each patient were included. A total of 35 panoramic radiographs were excluded due to poor exposure. This resulted in a sample of 152 panoramic radiographs from 24 patients with Apert syndrome (eight boys and 16 girls) and 35 patients with Crouzon syndrome (18 boys and 17 girls) born from 1970 to 2004. The patients had an average of 2.5 radiographs (minimum two, maximum five, median two), and the time-interval between two single radiographs from a patient varied between 6.1 months and 2.2 years. The use of data from human subjects followed an approved protocol and satisfied the requirement of the institutional review board (approval number MEC-2010-304).

TABLE 2 Overview of the Diagnostic Genetic Mutations in Patients With Crouzon and Apert Syndromes (Wilkie et al., 1995; Mathijssen, 2000)

	Apert (n = 30)	*Crouzon (n = 42)*
FGFR2		
P253R	12	
S252W	18	
A362T		3
C278F		5
C342R		2
C342T		2
C342W		3
C342Y		8
G271V		1
G338R		1
Q289P		3
S267P		3
S354C		2
W290R		4
Y105C		1
Y340H		3
FGFR3		
A391E		1

Control panoramic radiographs were obtained from normal children evaluated between 1971 and 1976 who participated in the mixed-longitudinal Nijmegen Growth Study (Prahl-Andersen et al., 1979). Only children with similar ages as the syndromic patients were used as controls. The controls consist of three mixed-longitudinal cohorts who were followed for 5 years, from 4 to 14 years of age. At the start of the study, the children were 4, 7, or 9 years of age. A total of 2151 panoramic radiographs of 327 children (157 boys and 170 girls; age range, 7.5 to 14 years) were selected. On average, 6.5 radiographs (minimum two, maximum 12, median eight) were used for each individual, with a time interval of 6 or 12 months between every two radiographs. The control radiographs

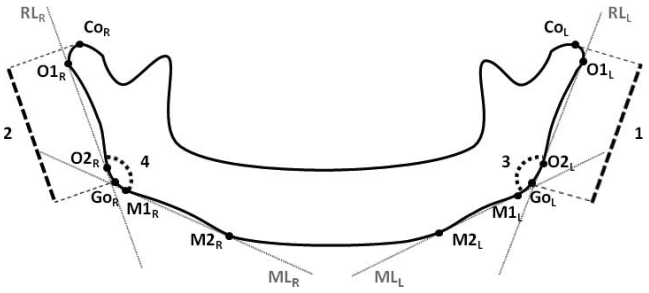

FIGURE 2 Mandibular landmarks, lines, and measurements used for asymmetry (Habets et al., 1987). Landmarks and lines: Co = most superior point of the condylar image; O1 = most superior point of the condyle; O2 = most lateral point of the ascending ramus; Go = gonion; a point on the bony contour of the mandibular angle determined by bisecting the line of the posterior border of the mandibular ramus and the line of the lower border of the mandibular body angle; M1 = most inferior point of the mandibular angle on the tangential line of the lower border of the mandibular body; M2 = most inferior point of the ascending lower border of the mandible; RL-line = tangential line of the posterior border of the mandibular ramus trough the points O1 and O2; ML-line = tangential line of the lower border of the mandibular body through the points M1 and M2.Measurements: 1,2. Condylar-ramal height left (L) and right (R), respectively; the distance between landmarks condylion and gonion; 3,4. Gonial angle left (L) and right (R), respectively; angle in degrees between tangential line of the posterior border of the mandibular ramus and tangential line of the lower border of the mandibular body.

were collected using a standardized procedure, using different panoramic machines: Philips OrthOralix (Eindhoven, The Netherlands), Siemens Orthopantomograph (Erlangen, Germany), and Siemens Orthophos. The magnification factor varied between 1.28 and 1.33. The conventional panoramic radiographs were scanned and digitized for further analysis.

Measurements

Twelve landmarks were digitized using Viewbox software (v3.1.1.14, D. Hal 1995–2006, Athens, Greece) (Fig. 2a and 2b). Only angular and ratio measurements were used due to magnification differences. An established method for measuring condylar and ramal asymmetry on panoramic radiographs was used (Habets et al., 1987; Habets et al., 1988). The measurements have been used for quantifying both directional and fluctuating asymmetry (Van Valen, 1962; Melnik, 1992; Liukkonen et al., 2005) (Fig. 2). Condylar-ramal heights and gonial angles were used to calculate mandibular asymmetry based on the differences between the left (L) and right (R) sides. Directional and fluctuating asymmetry were calculated according to the formulae in Table 1.

Statistical Analysis

Intrareliability and Interreliability

One investigator performed all of the measurements. Intraexaminer error for reproducibility of the measurements was determined by retracing panoramic radiographs from 23 syndromic patients (n = 107) and 20 control children (n = 122), with an interval of 2 weeks between replicates. Interexaminer error was determined by two investigators retracing panoramic radiographs from 20 syndromic patients (n = 20) and 20 control children (n = 20), also with an interval of 2 weeks between replicates. Interclass correlation coefficients were calculated (Shrout and Fleiss, 1979). For the statistical analyses the SPSS software package (version 15.0, SPSS, Chicago, IL) was used.

Growth Models

Orthogonal polynomials were used to model directional and fluctuating asymmetry over time. The mathematical description of the procedure is given by Grizzle and Allen (1969), and extended by Goldstein (1986). The program MLwiN (version 2.1, Centre for Multilevel Modelling, London, U.K.) was used to model growth changes and compare the three groups. For each y variable (asymmetry measurement), a polynomial equation was estimated for the patient (i) on the age of measurement (j). For each y variable of directional and fluctuating asymmetry (condylar-ramal height and gonial angle) a polynomial equation was estimated. The y intercept was adjusted to 10 years of age (intercept = age 10) to provide a comparison in the middle of the age range and to reduce the complexity of the computations. Average growth curves were estimated between 7.5 and 14 years of age. Due to expected group differences, separate models were fitted for each group. A cubic model was first fitted for each group and the highest order term was checked for statistical significance by using the t test. Statistical significance was determined by the standard errors of the estimates, using a .05 level for statistical significance. If the term was not significant, it was removed and a new reduced model was fitted. Because there were no statistically significant differences between the two sexes, boys and girls were pooled. The initial equation was:

$$y_{ij} = \}\beta_{0ij}\text{constant} + \}\beta_1 t_{ij} + \}\beta_2 t_{ij}^2 + \}\beta_3 t_{ij}^3,$$

with $\}\beta_{0ij} = u_{0j} + e_{0ij}$.

The asymmetry growth measurement, y was computed by adding the intercept ("β_{0ij}) to the products of other fixed coefficients ("β_1, "β_2, and "β_3) multiplied by age (t) at each occasion. The u_{0j} and e_{0ij} comprise the random portion of the model and are assumed to have means equal to zero, to be uncorrelated, and to be normally distributed. The level 1 residual e_{0ij} represents within-subjects variation, or the error term; whereas, the level 2 residual u_{0j} represents between-subjects variation (Goldstein, 1986).

The polynomial model takes full advantage of each patient's individual longitudinal growth data and

TABLE 3a Ratios of Fluctuating Asymmetry; Estimated Intercepts and Linear Coefficient at the Age of 10 Years in Three Groups (Crouzon, Apert, and Control Subjects)

	Apert		*Crouzon*				*Controls*			
	Intercept		*Intercept*		*Linear*		*Intercept*		*Linear*	
Measures	*Estimate (SE)*	*t Value*	*Estimate (SE)*	*t Value*	*Estimate (SE)*	*t Value*	*Estimate (SE)*	*t Value*	*Estimate (SE)*	*t Value*
Condylar-ramal height	4.244e-2 (5.020e-3)	8.454***	4.554e-2 (4.114e-3)	11.080***	−5.418e-3 (1.665e-3)	−3.254**	3.193e-2 (8.737e-4)	36.546***		
Gonial angle	3.468e-2 (5.060e-3)	6.854***	2.761e-2 (2.526e-3)	10.930***			2.233e-2 (7.588e-4)	30.706***	7.302e-4 (2.884e-4)	2.532*

* $P < .05$; ** $P < .01$; *** $P < .001$.

statistically evaluates the shape of the curve. Iterative generalized least squares were used to estimate the model's parameters (Goldstein, 1986).

Results

Measurement Error

The interclass correlation coefficient for intrainvestigator reliability varied from .95 to .99 for condylar-ramal height and gonial angle, respectively. The interclass correlation coefficient for interinvestigator reliability varied from .89 to .99.

Growth Models

Controls

The multilevel procedures showed that the growth followed simple models, ranging from constant (i.e., no growth) to linear changes over time. The fixed terms of each model were used to estimate the values for fluctuating and directional asymmetry between 7.5 and 14 years of age. For instance, the directional asymmetry for the gonial angle in the control group had a ratio of 0.00965 at the age of 12 years, computed as $0.00783 + (0.00091 \times 2)$ (Table 3b). The linear term 0.00091 (the yearly change) was multiplied by 2 instead of 12 because the intercept was set to 10 years of age. Multilevel growth models showed for the fluctuating asymmetry in the control group no change over time for condylar-ramal height and a slight increase for the gonial angle (Fig. 3a and 3b). For the directional asymmetry, condylar-ramal height showed dominance for the right side and there was no change over time (Fig. 4a). However, for the gonial angle, the controls showed an increase of directional asymmetry, with dominance to the mandibular left side (Fig. 4b).

Patients With Crouzon Syndrome

Fluctuating asymmetry measurements for condylar-ramal height decreased between 7.5 to 14 years of age (Fig. 3a). At 10 years of age, statistically significant more fluctuating asymmetry for condylar-ramal height was found compared with controls (Tables 3a and 4a). Fluctuating asymmetry for the gonial angle did not change over time (Fig. 3b), and no differences with controls were seen at the age of 10 years. For patients with Crouzon syndrome, the condylar-ramal height had dominance for the right side (Fig. 4a) and the directional asymmetry decreased between 7.5 and 14 years of age (Fig. 4a). At the age of 10 years the condylar-ramal height showed statistically significantly more directional asymmetry compared with the controls ($t = -2300$, $P < .05$) (Tables 3b and 4b). The gonial angle of the patients with Crouzon syndrome showed dominance for the mandibular left side (Fig. 4b) and no statistically significant differences were found with controls (Tables 3b and 4b).

Patients With Apert Syndrome

Measurements for fluctuating asymmetry (condylar-ramal height and gonial angle) were statistically significantly higher in Apert patients compared with the controls (Table 4a). Measurements for fluctuating asymmetry did not change in the period between 7.5 and 14 years of age (Figs. 3a and 3b). Patients with Apert syndrome showed no statistically significant directional asymmetry for the condylar-ramal height and gonial angle (Table 3b), and these measurements did not change over time (Figs. 4a and 4b). The controls showed statistically significantly more directional asymmetry for gonial angle compared with Apert patients ($t = 2328$, $P < .05$) (Table 4b). No statistically significant differences were found for the condylar-ramal height between these two groups (Table 4b).

Patients With Crouzon Syndrome Compared With Patients With Apert Syndrome

Multilevel modeling showed different tendency of growth over time (constant versus linear curves) for patients with Crouzon syndrome compared with patients with Apert syndrome (Figs. 3a and 4a). Although

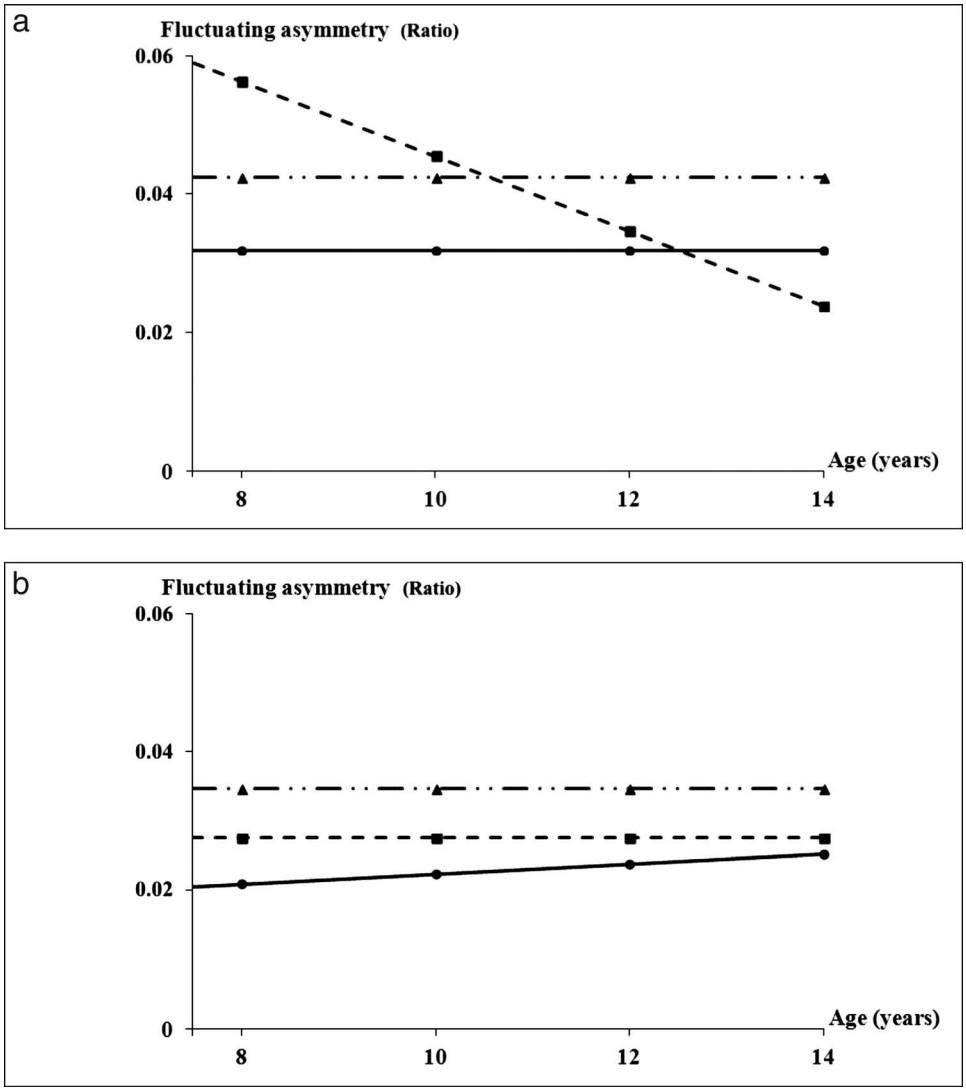

FIGURE 3 **a: Ratios of fluctuating asymmetry for condylar-ramal height for control subjects (•), patients with Crouzon (■) and Apert (▲) syndromes. b: Ratios of fluctuating asymmetry for gonial angle for control subjects (•), patients with Crouzon (■) and Apert (▲) syndromes.**

the two groups showed different growth models, no statistically significant differences were found between the two syndromes for either directional or fluctuating asymmetry (Tables 4a and 4b).

Discussion

The most important finding in this study was that fluctuating asymmetry was larger in patients with Apert syndrome than in controls and patients with Crouzon syndrome. Increased fluctuating asymmetry for condylar-ramal height and for the gonial angle may imply more developmental instability in patients with Apert syndrome (Table 4a; Fig. 3a and 3b). Previous studies showed increased fluctuating asymmetry in other syndromes or anomalies, such as Down syndrome and cleft lip and palate (Adams and Niswander, 1967; Barden, 1980; Laspos et al., 1997; Kurt et al., 2010). Patients with Crouzon syndrome showed less developmental instability based on condylar-ramal height and gonial angle compared with patients with Apert syndrome (Table 4a). Craniofacial discrepancies in both syndromes hardly change with growth and development, probably due to the genetic influence (Parsons, 1992). Differences in craniofacial morphology between Crouzon and Apert syndromes showed more severe abnormal growth pattern among the latter group, which concurs with previously reported results (Costaras-Volarich and Pruzansky, 1984; Kreiborg and Cohen, 1998).

Fluctuating asymmetry during growth in patients with syndromic craniosynostosis is influenced by genetic and environmental factors. There is evidence that genetic and environmental disturbances contribute to increase fluctuating asymmetry (Parsons, 1992). These patients are confronted with different stress factors over time. The stress factors include physical, emotional, and social problems, probably partly caused by their craniofacial

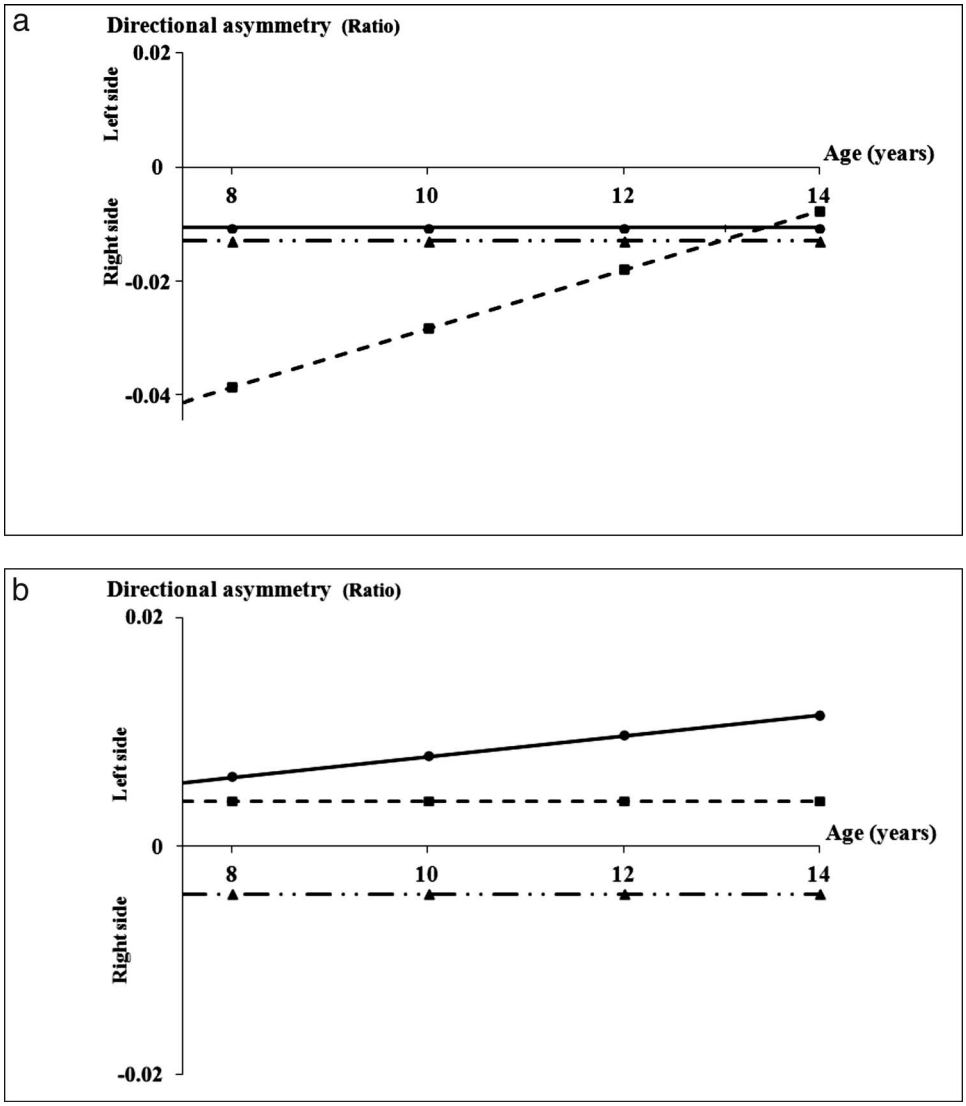

FIGURE 4 a: Ratios of directional asymmetry for condylar-ramal height for control subjects (•), patients with Crouzon (■) and Apert (▲) syndromes. b: Ratios of directional asymmetry for gonial angle height for control subjects (•), patients with Crouzon (■) and Apert (▲) syndromes.

disfigurement (Campis, 1991; Furlow et al., 1997; De Jong et al., 2012). Also several surgical or other medical interventions like long-term orthodontic treatment during growth could be a major stress factor for these patients. The overall effect of these stress factors may explain the higher degree of fluctuating asymmetry of the mandible found for patients with Crouzon and Apert syndromes compared with the control group.

Directional asymmetry in a growing patient with syndromic craniosynostosis was expected. A dominant side of a structure can be explained by growth discrepancies caused by craniosynostosis and etiological factors. Etio-

TABLE 3b Ratios of Directional Asymmetry; Estimated Intercepts and Linear Coefficient at the Age of 10 Years in Three Groups (Crouzon, Apert, and Control Subjects)

	Apert		*Crouzon*				*Control*			
	Intercept		*Intercept*		*Linear*		*Intercept*		*Linear*	
Measures	*Estimate (SE)*	*t Value*	*Estimate (SE)*	*t Value*	*Estimate (SE)*	*t Value*	*Estimate (SE)*	*t Value*	*Estimate (SE)*	*t Value*
Condylar-ramal height	−1.297e-2 (1.003e-2)	−1.293	−2.840e-2 (6.507e-3)	−4.365***	5.164e-3 (2.248e-3)	2.297*	−1.064e-2 (1.650e-3)	−6.448***		
Gonial angle	−4.172e-3 (8.605e-3)	−0.485	3.931e-3 (4.893e-3)	0.803			7.833e-3 (1.341e-3)	5.841***	9.066e-4 (3.885e-4)	23.340***

* $P < .05$; *** $P < .001$.

TABLE 4a Ratio Differences in the Fluctuating Asymmetry Between Groups; Estimates Differences, SE, and *t* Values

	Apert Minus Control		*Crouzon Minus Control*		*Apert Minus Crouzon*	
	Intercept		*Intercept*		*Intercept*	
Measures	*Estimate (SE)*	*t Value*	*Estimate (SE)*	*t Value*	*Estimate (SE)*	*t Value*
Condylar-ramal height	1.049e-2 (4.153e-3)	2.526*	8.760e-3 (3.351e-3)	2.614*	−1.729e-3 (6.378e-3)	−0.271
Gonial angle	1.169e-2 (3.228e-3)	3.621**	4.464e-3 (2.568e-3)	1.807	7.394e-3 (5.241e-3)	1.411

* $P < .05$; ** $P < .01$.

logic factors that could explain the mandibular asymmetry of Crouzon and Apert syndromes include condylar pathologies, functional habits, and dental malocclusions (Costaras-Volarich and Pruzansky, 1984; Kreiborg and Cohen, 1998). The controls showed a dominant side (left or right) for directional asymmetry (Table 3b; Fig. 4a and 4b), which is in line with previous studies (Peck et al., 1991; Melnik, 1992). The Crouzon patients showed a higher degree of directional asymmetry for condylar-ramal height over time compared with the controls. Premature unilateral synostoses of calvarial sutures may explain the directional asymmetry that occurs in these syndromic patients (Cohen and Kreiborg, 1990) and may indirectly influence the growing mandible (Costaras-Volarich and Pruzansky, 1984).

However, for the other measurements of the syndromic patients only a tendency of directional asymmetry was found, this in contrast to controls (Table 3b). The small average value of directional asymmetry close to zero could be misleading (Fig. 1a). It is reasonable to consider that in Crouzon and Apert syndromes the more rare type of antisymmetry may occur (Fig. 1b). In contrast to directional asymmetry where the direction of asymmetry is either left or right, antisymmetry shows right-sided and left-sided bimodal distribution. Antisymmetry may show a wide range of individual asymmetry in patients. A possible explanation for the present results in this study could be the wide range of asymmetry in patients demonstrated by the large standard error found for both syndromes (Palmer and Strobeck, 1986) (Table 3b). However, after analyzing scatter plots for the actual distribution of the results, the syndromic patients showed no bimodal distribution for the condylar-ramal height or for the gonial angle. Further research into mandibular antisymmetry is needed. The possible role of bimodal distribution in the facial symmetry of bilateral structures in these patient groups should be studied. We think that the surgical interventions mentioned do not influence the outcomes of our study, but this needs to be examined further. New technological methods like three-dimensional reconstructions of computed tomography images or laser surface-scanning methods could be a helpful tool for assessing facial asymmetry or other bilateral structures (DeLeon and Richtsmeier, 2009; Djordjevic et al., 2011)

For reliable and accurate measurements on panoramic radiograph, some recommendations from the literature were used in this study. Reliable vertical and angular measurements were used instead of inaccurate horizontal measurements (Habets et al., 1987; Kambylafkas et al., 2006; Elslande et al., 2008). Ratios instead of absolute values were used to prevent positioning, distortion, or magnification errors due to the use of different panoramic x-ray machines (Fig. 2) (Habets et al., 1988; Kjellberg et al., 1994). In addition, regarding the adopted statistical methodology, multilevel models offer an important tool for describing longitudinal development of asymmetry with limited data of rare syndromes like Crouzon or Apert. Both individual and average growth curves can be described; it is a flexible model because it uses polynomials, which can describe growth curves of almost any form (Goldstein, 1986). Conventional procedures, including cross-sectional descriptions and analyses of yearly velocities from two measurement occasions provide less optimal use of the available material. Other polynomial methods would have required elimination of most of the subjects, due to missing observations and/or adjustment of values to exact ages (Goldstein, 1986).

TABLE 4b Ratio Differences in the Directional Asymmetry Between Groups; Estimates Differences, SE, and *t* Values

	Apert Minus Control		*Crouzon Minus Control*		*Apert Minus Crouzon*	
	Constant		*Constant*			
Measures	*Estimate (SE)*	*t Value*	*Estimate (SE)*	*t Value*	*Estimate (SE)*	*t Value*
Condylar-ramal height	−8.7806e-4 (7.2784e-3)	−1.206	−1.360e-2 (5.913e-3)	−2.300*	1.232e-2 (1.114e-2)	1.081
Gonial angle	−1.298e-2 (5.575e-3)	−2.328*	−4.638e-3 (4.439e-3)	−1.056	−8.271e-3 (9.267e-3)	−0.893

* $P < .05$.

Conclusion

The following conclusions can be made from this study:

(1) Fluctuating asymmetry in patients with Apert syndrome was statistically significant higher compared with controls.
(2) No statistically significant differences were found for longitudinal directional and fluctuating asymmetry between patients with Crouzon or Apert syndrome.
(3) Findings of fluctuating and directional asymmetry may illustrate the influence of genetic and environmental factors in growth and development of children with Crouzon or Apert syndrome.
(4) Further research is needed to investigate the possible impact of different stress factors induced by medical interventions or other environmental factors on patients with Crouzon or Apert syndrome over time.

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