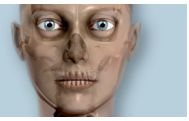
Orthodontics & Craniofacial Research



ORIGINAL ARTICLE

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Short mandible – a possible risk factor for cleft palate with/without a cleft lip

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Structured Abstract

Objectives – To estimate the influence of a short mandible on the risk of developing a cleft palate with/without a cleft lip (CP).

Setting and sample population – The retrospective sample consisted of 115 2-month-old Danish infants with CP, and 70 control infants with unilateral incomplete cleft lip (UICL).

Material and Methods – Cephalometric X-rays were obtained. Mandibular length (L_m) was measured and corrected for body length (L_b) to remove influence of varying body length in the sample. Logistic regression was applied to the corrected mandibular length (L_{mc}) to calculate the risk of having a cleft palate.

Results – The mean mandibular length in the group with CP was about 4 mm shorter than in the control group. Odds ratio (OR) was calculated to be 0.58 (95% confidence interval 0.48–0.68), implying that an individual's risk of cleft palate with/without a cleft lip increases about 50% per mm decrease in mandibular length.

Conclusions – A special facial type including a short mandible is a possible risk factor for cleft palate, and it was found that the risk of cleft palate increases 58% per mm decreases in mandibular length.

Key words: cleft palate; mandible; risk factor

Introduction

Numerous studies have suggested non-syndromic cleft lip and palate is caused by a combination of genetic and environmental factors, and it has been assumed the genetic component is polygenic (1). However, despite several thorough genetic studies, a major gene or locus causing the condition has not yet been identified. The etiology of cleft lip and palate is therefore still, usually, explained by means of a multifactorial model (2).

According to the multifactorial model, a predisposition or liability in an individual to cleft lip and palate determined by genetic and environmental factors will make it likely that a cleft malformation occurs. If the total of predisposing factors exceeds a particular threshold value, the individual will develop a cleft malformation.

Predisposing environmental factors suspected to play a role in the etiology of cleft lip and palate are maternal vitamin, alcohol consumption, and smoking habits (e.g. 3–5). In this context, it is, however, noteworthy that the prevalence of both non-syndromic cleft lip (CL) with and without cleft palate and isolated cleft palate (ICP) has been shown to be nearly constant in the Danish population during a 40-year period (4), despite raising maternal age and intensive information campaigns about the effects of alcohol consumption and smoking, as well as the importance of vitamin supplements during pregnancy.

In previous work, we have carried out a comprehensive three-projection cephalometric assessment of craniofacial morphology in infants with un-repaired non-syndromic cleft palate with/without a cleft lip [unilateral complete cleft lip and palate (UCCLP), bilateral complete cleft lip and palate (BCCLP), isolated cleft palate (ICP) and Robin sequence (RS)] and compared them to a control group of infants with un-repaired unilateral incomplete cleft lip (UICL) (6–15). These studies showed cleft palate with/without a cleft lip is most likely a localized malformation and not a craniofacial anomaly as the size and shape of the calvaria, the cranial base and the orbits are, in general, within normal limits.

In combination, these studies also showed all the subgroups with CP are characterized by a short and retrognathic mandible. The studies have led us to the formulation of the hypothesis that an inherited special facial type including a short and retrognathic mandible may predispose for developing a cleft palate.

Furthermore, animal studies have suggested a causal relation between a short and retrognathic mandible and induction of CP (16–18). In those studies, an inhibition of fetal mandibular growth was induced in animals without a genetic disposition to cleft malformations, and this was shown to result in the development of a cleft palate in many cases.

Treating mandibular length as a possible risk factor for developing cleft palate, it is interesting to assess the risk of developing cleft palate based on the actual mandibular length in an individual.

The overall goal of this study was therefore to present the mandibular lengths in different groups with CP and compare them to a control group with UICL, as well as to estimate the influence of a short mandible on the risk of developing cleft palate. The study adds to the current understanding of why cleft palate occurs and draws the attention of researchers in the field to consider the possibility that the reason for the presently many non-conclusive genetic studies may be related to the fact that not all factors predisposing for cleft palate have been thoroughly investigated.

Material and methods

The sample

The infants included in the present study were drawn from a group representing all Danish cleft infants born 1976–1981 (19). For the present study, 115 infants with non-syndromic CP (45 with UCCLP; 19 with BCCLP; 51 with ICP), and 70 infants with incomplete unilateral cleft lip (UICL) (control group) were enrolled. It should be noted that all infants with ICP had a cleft involving the hard palate, and infants with RS were not included in this study. All infants were examined at 2–3 months of age (70–100 days) before any type of treatment. There was no statistically significant difference in mean age between the two groups.

Body weight

There was no statistically significant difference in mean body weight between the CP group and control group at birth. At 2 months of age, the mean body weight was significantly lower in the group with CP compared with the control group.

Body length

There was no statistically significant difference in mean body length (L_b) between the CP group and the control group, neither at birth nor at 2 months of age.

Cephalometric X-rays

A three-projection infant cephalometric unit was used for the current investigation [the unit was developed and described in detail by (20)]. For the present study, only the lateral cephalogram was used. The magnification of the midsagittal plane was 5.6%. Measurements were corrected for magnification.

Variables

The landmarks *condylion* and *prognathion* were digitized in all subjects (6). The total mandibular length (L_m) from *condylion* to *prognathion* was calculated in all infants.

Statistical methods

The mandibular length (L_m) was regressed onto the body length (L_b) providing the linear correlation coefficient R with 95% confidence interval (CI). The regression was carried out separately for the two groups, resulting in two regression lines. The significance of the difference between the two groups (difference in slope and *y*-intercept of the two regression lines) was tested using ANCOVA. The mandibular length (L_m) was corrected for body length (L_b) to remove the influence of varying body length in the sample.

The corrected mandibular length (L_{mc}) was estimated as the effective mandibular length at the mean body length ($\bar{L}_b$) of the sample. This corresponded to moving each data point in the regression plot parallel to a regression line until intersection with $x = \bar{L}_b$. The corrected values were estimated as $L_{mc} = \bar{L}_m + L_m - aL_b + b$, where $\bar{L}_m$ is the mean mandibular length in the sample, and a and b are the slope and *y*-intercept of the line, respectively.

ANOVA was applied to test for differences between means of several groups. Logistic regression was applied to values of corrected mandibular length in order to calculate the risk of cleft palate. Standard logistic regression was performed using *Diagnosis* as the dichotomous response variable (0 = UICL; 1 = CP), and L_{mc} as the continuous explanatory variable. An odds ratio (OR) with 95% Wald confidence limits was calculated. A standard likelihood ratio (LR) test and Wald test (WT) were performed on the logistic model. Whenever possible, it is desirable to confirm the logistic regression result using independent data. This was achieved by splitting data into two independent halves and performing logistic regression on each of the two subsets separately, allowing comparison of independent results of OR, LR and WT.

Normal curves were fitted to histogram distributions of L_{mc}, and departure from normal distribution was estimated by goodness-of-fit tests including Shapiro–Wilk (W) and Kolmogorov–Smirnov (D) test statistics. A bimodality coefficient (SAS Version 9.3 documentation) was calculated according to

$$B = \frac{m_3^2 + 1}{m_4 + \left[\frac{3(\mathbf{n}-1)^2}{(\mathbf{n}-2)(\mathbf{n}-3)}\right]}$$

where m_3 and m_4 are skewness and kurtosis, respectively. Values of b greater than 0.555 (the value for a uniform population) indicates a bimodal distribution.

The statistical analyses were performed using SAS Version 9.3 (SAS Institute Inc., Cary, NC, USA).

Error of the method

An intra-rater reproducibility was estimated using duplicate landmarking of $n = 30$ individuals. The method error, $s(i)$, encompassing both systematic and random errors, was calculated according to Dahlberg's formula (21):

$$s(i) = \sqrt{\sum d^2/2\mathrm{n}} \quad \text{where } d = L_{m1} - L_{m2},$$

L_{m1} and L_{m2} being the mandibular length at first and second measurement, respectively.

Institution/ethics board approval

At the time the material was collected, no national ethics review committee/institutional review board (IRB) was established in Denmark. However, all data used in this study were obtained in a clinical context as part as a standardized treatment regime with full acceptance from the parents and fully follows the World Medical Association Declaration of Helsinki (1975, as revised in 1983).

Results

Figure 1 summarizes the findings of mean mandibular length in the ICP, BCCLP, and UCCLP groups compared with a control group of UICL.

Figure 2 shows the result of regressing the mandibular length onto the body length. The correlation coefficient for the CP group was $R = 0.56$ [95% CI: (0.42,0.67)] and for the control group, $R = 0.52$ [95% CI: (0.33,0.67)].

ANCOVA showed no significant difference between the slopes of the two regression lines ($p = 0.7$), and hence, a common regression line $y = ax + b$ was used for calculating L_{mc}, with $a = 0.558$ and $b = 18.51$. The regression line used (dash-dotted line in Fig. 2) represents the linear discriminant function that best separates the two groups after correcting for mean mandibular length in the groups.

Table 1 summarizes the values of L_{mc} for the two groups, for the total group, and for the three subgroups of CP (UCCLP, ICP and BCCLP). Mean L_{mc} was 53.7 mm and 49.6 mm for the UICL and CP group, respectively, implying a statistically significant difference between the means of 4.1 mm (Student's t-test, $p < 0.0001$; non-different variances). No statistically significant difference ($p = 0.091$) was found between the mean values of L_{mc} between the three subgroups of CP (UCCLP, ICP and BCCLP), thus justifying pooling these into one group.

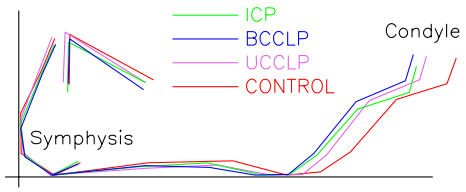

Fig. 1. Superimposed mean plots of the mandible in 2-month-old infants with un-repaired ICP, BCCLP, and UCCLP, respectively, and an age-matched control group with UICL.

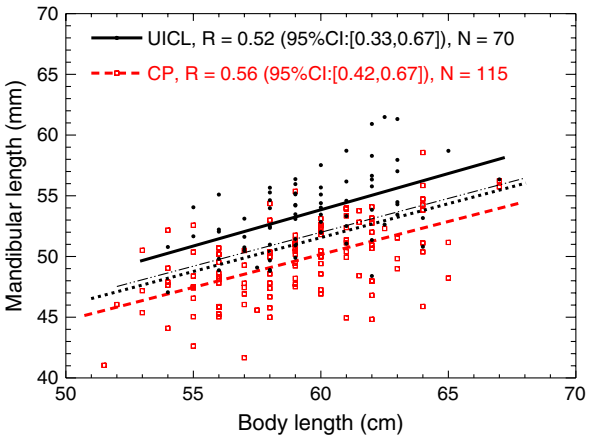

Fig. 2. Plot of mandibular length (L_m) vs. body length (L_b). Regression lines for the two groups are shown, as indicated. The dotted line represents a pooled (UICL and CP) dataset, while the dash-dotted line represents a linear discriminant function that best separates the two groups.

Table 1. **Descriptive statistics, as indicated, for various groups and subgroups**

	Group	N	Mean	Max	Min	SD	*p*-value
(a)	All	185	51.14	61.48	41.04	3.71	
(b)	Control (UICL)	70	53.65	61.48	47.05	3.09	<0.0001(*)
(c)	CP (ICP + UCCLP + BCCLP)	115	49.61	58.56	41.04	3.20	
(d)	UCCLP	45	50.43	55.85	45.04	2.72	
(e)	ICP	51	49.12	58.56	41.04	3.41	0.091(!)
(f)	BCCLP	19	49.02	54.26	41.67	3.44	

(*) indicates *p*-value obtained from Student's *t*-test. (!) indicates *p*-value obtained from ANOVA.

Figure 3 shows histograms of L_{mc} in the CP group and UICL group, as well as in the total group and UCCLP, ICP, and BCCLP subgroups, respectively.

Results of tests for normality and bimodality are presented in Table 2. The *p*-values of the Shapiro–Wilk and Kolmogorov–Smirnov test were both >0.15, thus not rejecting the hypothesis of normally distributed data in all groups tested. The bimodality coefficient was below 0.555 in all three cases, thus providing no evidence of bimodality.

The result of the logistic regression is shown in Fig. 4. The odds ratio (OR) was 0.58 with 95% Wald confidence limits 0.48–0.68, implying that an individual's risk of cleft palate with/without a cleft lip increases about 50% per mm decrease in the mandibular length. Both the likelihood ratio (LR) and Wald test (WT) resulted in *p*-values < 0.0001, providing evidence for a good model fit to the data. Results are summarized in Table 3 together with the results of logistic regression using two independent halves of the data as input, respectively. The latter results confirmed a risk increasing about 50% per mm, again with LR and WT *p*-values <0.0001.

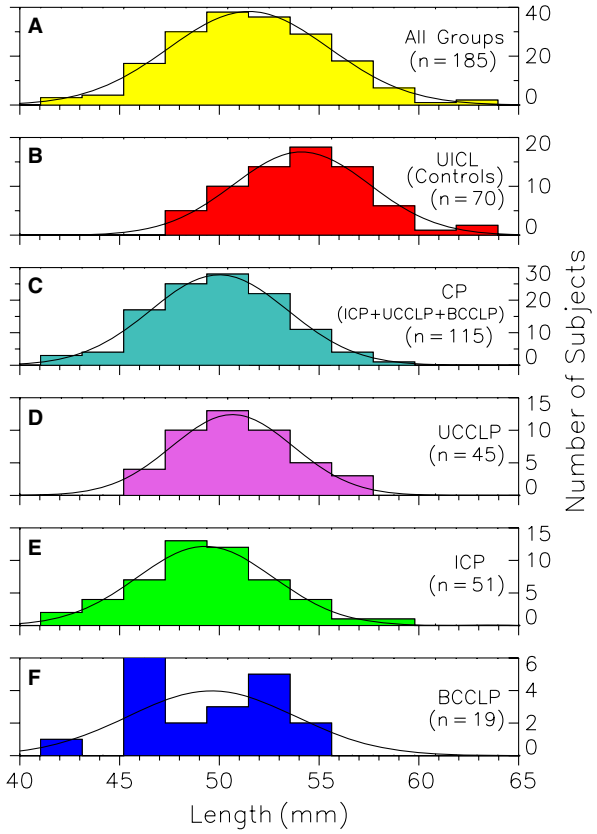

Fig. 3. Histograms of L_{mc} for the same groups and subgroups as for which descriptive statistics are given in Table 1. (a) All groups (UCCLP, BCCLP, ICP, and UICL) pooled. (b) The control group with UICL. (c) All groups with cleft of the secondary palate (UCCLP, BCCLP, and ICP) pooled. (d) UCCLP. (e) ICP. (f) BCCLP. Colors correspond between this Figure and Fig. 1. Fitted normal curves are shown overplotted on the histograms.

Method error

The error of the method was 0.6 mm and was thus found to be within acceptable limits.

Discussion

In the present study, a group of infants with UICL (the least severe form of CL) was used as control group. The deviations in the morphology of the facial skeleton in subjects with CL are by other investigators shown to be very mild and to primarily affect the cleft region. (22–28).

Based on these findings, the UICL group has in the present study been considered as a usable normative control group, as it was not considered ethically acceptable to enroll completely normal children due to the X-ray exposure and the need for sedation (all X-rays used in the

Table 2. **Results of tests for normality and bimodality. *W*(*P*) provides the Shapiro–Wilk test statistic W and its corresponding *p*-value. *D*(*P*) provides the Kolmogorov–Smirnov test statistic D and its corresponding *p*-value. m_3 and m_4 are the kurtosis and skewness, respectively. *b* is the bimodality coefficient**

Group	*W* (*P*)	*D* (*P*)	m_3	m_4	*b*
All	0.9956 (0.866)	0.0284 (>0.15)	0.101	0.105	0.32
Control (UICL)	0.9837 (0.496)	0.0472 (>0.15)	0.121	0.379	0.35
CP (ICP + UCCLP + BCCLP)	0.9951 (0.960)	0.0530 (>0.15)	0.0169	−0.0213	0.32

Table 3. **Results of logistic regressions. Inputs are either the 'Full' dataset (upper row) comprised of n0 = 70 with diagnosis = 0 (controls) and n1 = 115 with diagnosis = 1, or two independent halves (two lower rows) created by splitting the full dataset in two parts by extraction of every other data value (omitting one data value with diagnosis = 1 to obtain the same size of the two datasets). OR is the point estimate of the odds ratio, 95% CI provides the Wald confidence interval, while *P* (LR) and *P*(WT) are the *p*-values of the likelihood ratio and Wald tests, respectively**

Input	n0	n1	OR	95% CI	*P*(LR)	*P*(WT)
Full	70	115	0.575	0.484–0.683	<0.0001	<0.0001
First-Half	35	57	0.538	0.413–0.702	<0.0001	<0.0001
Second-Half	35	57	0.610	0.489–0.762	<0.0001	<0.0001

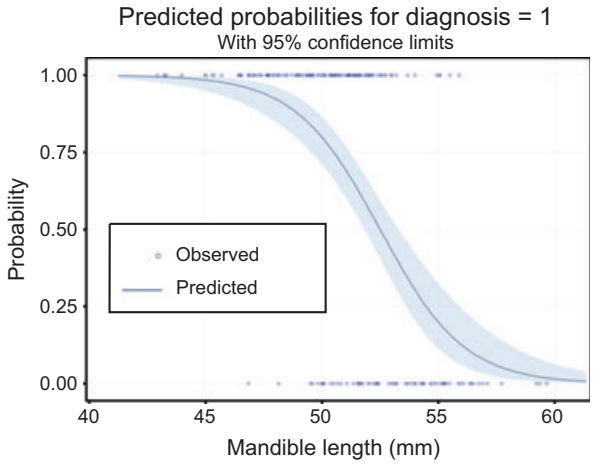

Fig. 4. Results of logistic regression showing the probability of having CP (Diagnosis = 1) as a function of corrected mandibular length (L_{mc}). Gray region represents 95% confidence area.

study were obtained as part of a standardized treatment system in a clinical context).

Many previous studies on the facial morphology have shown that a short and retrognathic mandible is typical for individuals with clefting of the secondary palate with/without a cleft lip. The short mandible seems to be independent of the age of the individual and has been reported in studies on untreated infants with non-syndromic clefts of the secondary palate with/without a cleft lip (7–15, 29, 30), as well as on older age groups (e.g. 22, 31–40).

Experimental studies have also suggested a causal relation between micrognathia and flexed head posture in the fetus and the induction of CP (16–18, 41–46). These studies show that the etiology of cleft palate malformation can be related to interference with a number of different developmental events not primarily related to the palatal shelves.

Furthermore, Dahl et al. (30), as well as Kreiborg and Cohen (47), suggested that an intrinsic relationship between micrognathia and clefting of the secondary palate might exist.

It may be discussed whether the short mandible leads to the cleft, or if it is the cleft that leads to the short mandible. However, according to the literature (42, 48, 49), it has been shown that during mammalian secondary palate formation (in the chondrocranial period), the sagittal growth of the lower face is more rapid than that of the upper face, when Meckel's cartilage growth protrudes the mandible with attached tongue. Having this in mind, it would seem more likely that the short mandible impacts the development of the cleft and not the other way around.

Although the present study does not prove a causal relationship between a short mandible and the development of the cleft palate, it seems, together with previous studies from our group on untreated infants with cleft palate with/without a cleft lip, to support the hypothesis that individuals with cleft palate with/without a cleft lip have a special facial type, including a rather short mandibular length (7–15). However, we are not claiming that the mandible is abnormal in any way. Rather we are dealing with normal variation. The tests for normality (Table 2) showed good fit to a normal distribution. Furthermore, the bimodality coefficient for the combined group did not indicate the presence of two underlying populations. It may also be noted that we have previously shown that the velocity of mandibular growth in children with cleft palate from 2 to 22 months of age is normal (15).

The risk of developing cleft palate given the actual mandibular length in an individual was

calculated without the need to determine the causality of the association between cleft palate and mandibular length. Describing this association in terms of a risk clarifies the strength of the association to researchers that are customized to work with risk analysis and epidemiology. It also draws the attention to the importance of continuing the investigation of possible predisposing factors of cleft palate. It is still most likely that both genetic and environmental factors are involved and that the non-syndromic cleft etiology should be explained by a multifactorial threshold model. It would in the authors' opinion be useful if geneticists were inspired to look for a 'short mandible gene' when investigating the genetics of cleft palate, as the short mandible could be a predictor of cleft palate.

Conclusion

This study supports previous findings implying that individuals with non-syndromic cleft palate with/without a cleft lip have a special facial type involving a short mandibular length. The mean mandibular length was 4 mm shorter in the CP group than in a control group of individuals with unilateral incomplete cleft lip (UICL), and an individual's risk of developing a cleft palate was seen to increase 58% per mm decrease in mandibular length.

Clinical relevance

Non-syndromic cleft lip and palate is the most common craniofacial anomaly; however, despite thorough studies, a major gene/gene locus has not yet been identified.

Our study suggests that individuals who develop a cleft palate with/without cleft lip have a particularly short mandible and that mandibular shortness predisposes the condition.

Translation of our results into clinical practice could support the aims to find a gene/gene locus and, possibly in a longer perspective, a cure for the condition. Furthermore, prenatal diagnosis of cleft palate is currently a difficult task, and translation of the results would make early treatment planning and parent education possible.

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