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Original research

A retrospective study on familial occurrence of cleft lip and/or palate☆

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ABSTRACT

Objective: The aim of this study was to assess whether familial occurrence has an influence on the state of patients with non-syndromic cleft lip and/or palate (NsCL/P).
Materials and methods: A retrospective analysis was performed, using medical records of 425 patients with NsCL/P who underwent integrated treatment in the Cleft Lip and Palate Center, University of the Ryukyus Hospital between 1994 and 2010. No affected subjects had accompanying defects or findings suggestive of a syndromic diagnosis.
Results: Of the total of 425 participants with NsCL/P, 82 (19.29%) presented a positive history of cleft in their families and 343 (80.70%) presented a negative history. In the distribution of the cleft types, the frequencies of cleft lip only (CLO), cleft lip and alveolar (CLA) ridge, cleft lip and palate (CLP), and cleft palate only (CPO) except submucous cleft palate, were 10.97%, 18.29%, 56.09% and 14.63% in familial cases, and 12.82%, 23.32%, 39.06% and 24.78% in sporadic cases, respectively. There were statistical differences in the cleft types by chi-squared test ($p = 0.038$), odds ratios and 95%CI (OR = 0.84, 0.74, 1.99, 0.52; 95%CI, 0.39–1.79, 0.40–1.36, 1.22–3.24, 0.27–1.01, respectively). We also examined the distribution of the cleft side as well as the parental and neonatal status at delivery. However, we did not find any significant differences.
Conclusion: Familial occurrence might have an influence on the cleft types.
Further research is needed to define the reasons for this influence.

1. Introduction

Cleft lip and/or palate (CL/P) is a common birth defect of complex etiology, for which there has been some modest success in finding genetic contributors using candidate gene association and sequencing approaches. Asian and American Indian populations have the highest reported birth incidence, at 1/500 or higher, while the reported incidence in European-derived populations is around 1/1100, and the reported incidence in African-derived populations is 1/2500 [1].

Oral clefts can also be divided into phenotypic subgroups based on embryology, recurrence risks and genetic associations; the three major subgroups are those that involve the lip only (CLO), the lip and the palate together (CLP) or those that involve the palate only (CPO). There is a precedent for grouping CLO and CLP into clefts of the lip and/or palate. Oral clefts can also be divided into non-syndromic (Ns) or syndromic based on the presence of other congenital anomalies, significant developmental delay or known etiologic causes. Approximately 10% of CLO, 30% of CLP and 40–60% of CPO are associated with one of over 500 described syndromes [2].

Evidence for genetic factors in NsCL/P has been shown by studies of familial recurrence [3], concordance in twins [4] and segregation analysis [5]. Evidence for environmental factors of NsCL/P includes an increased risk for NsCL/P with smoking [6], and possibly alcohol exposure during pregnancy [7]. There may also be a preventive effect on the development of NsCL/P when multivitamins including folic acid are taken during early pregnancy [8]. Multiple studies have investigated gene–environment interactions [9,10]. Thus the etiology of NsCL/P is heterogeneous and it represents a complex trait.

If a patient with NsCL/P has a positive family history, we consider that genetic factors may be relatively stronger in a heterogeneous etiology. In addition, we consider that stronger genetic factors have

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Table 1
Relationship between analyzed familial patients and their affected family members.

Degree	Relationship	*n*(ratio)	Ratio
First degree relative	Father	5(0.06)	0.36
	Mother	10(0.12)	
	Siblings	16(0.19)	
Second degree relative	Paternal grandmother	1(0.01)	0.20
	Maternal grandfather	1(0.01)	
	Maternal grandmother	1(0.01)	
	Father's siblings	3(0.04)	
	Mother's siblings	2(0.02)	
Third degree relative	Offspring of father's siblings	6(0.07)	0.14
	Offspring of mother's siblings	3(0.04)	
	Siblings of paternal grandfather	1(0.01)	
	Siblings of paternal grandmother	2(0.02)	
Fourth degree relative	Relative on father's side above fourth degree	7(0.08)	0.16
	Relative on mother's side above fourth degree	7(0.08)	
Unknown		20	0.24

an influence on the state of patients with NsCL/P, including cleft types, laterality and extension. Few reports have focused on cleft types and positive family history among patients with NsCL/P [11].

The aim of this study was to assess whether or not familial occurrence has an influence on the state of patients with NsCL/P.

Our result suggested that a positive family history of NsCL/P might be associated with a 2-fold higher risk of CLP (OR = 1.99, 95%CI, 1.22–3.24), compared to those of CLO, cleft lip and alveolar (CLA) ridge, and CPO. Laterality and extension, however were not associated with the state of clefts between NsCL/P and NsCL/P.

2. Materials and methods

2.1. Subjects

A retrospective analysis was performed of medical records of 425 patients with NsCL/P who underwent integrated treatment in the Cleft Lip and Palate Center, University of the Ryukyus Hospital between 1994 and 2010. A familial case was defined as a proband with NsCL/P and family history (FNsCL/P). A sporadic case was defined as a proband with NsCL/P and without family history (SNsCL/P). No affected subjects had accompanying defects or findings suggestive of a syndromic diagnosis. Cases of submucous cleft palate (SMCP) among CPO patients were excluded due to differences in etiology of soft and hard cleft palate with that of SMCP.

The sample number and the relationship between our analyzed FNsCL/P and their affected family members are shown in Table 1.

The study was approved by the ethics committee of University of the Ryukyus Hospital.

2.2. Statistical analysis

We performed the chi-squared test and Fisher's exact test to calculate *p* values for differences in distribution of clefts by types, sides and extension as well as the parental and neonatal status when delivered in FNsCL/P versus SNsCL/P, using JMP v9.

Table 2
Distributions of cleft types in familial and sporadic NsCL/P.

	FNsCL/P *n*(ratio)	SNsCL/P *n*(ratio)	*p*-Value*	Odds ratio	95%CI**
CLO	9(0.11)	44(0.13)	0.038***	0.84	0.39–1.79
CLA	15(0.18)	80(0.23)		0.74	0.40–1.36
CLP	46(0.56)	134(0.39)		1.99	1.22–3.24
CPO	12(0.15)	85(0.25)		0.52	0.27–1.01

* Chi-squared test.
** Confidence interval.
*** $p < 0.05$.

Table 3-1
Distributions of cleft laterality in familial and sporadic NsCLP.

	FNsCL/P *n*(ratio)	SNsCL/P *n*(ratio)	*p*-Value*	Odds ratio	95%CI**
UCLP	32(0.70)	90(0.67)	0.856	1.12	0.54–2.31
BCLP	14(0.30)	44(0.33)			

* Fisher's exact test.
** Confidence interval.

Table 3-2
Distributions of cleft laterality in familial and sporadic Ns CLO, CLA and CLP.

	FNsCL/P *n*(ratio)	SNsCL/P *n*(ratio)	*p*-Value*	Odds ratio	95%CI**
Unilateral (CLO, CLA and CLP)	51(0.73)	201(0.79)	0.754	0.76	0.42–1.39
Bilateral (CLO, CLA and CLP)	19(0.27)	57(0.22)			

* Fisher's exact test.
** Confidence interval.

Table 3-3
Distributions of complete and incomplete cleft types in familial and sporadic NsCLP.

	FNsCL/P *n*(ratio)	SNsCL/P *n*(ratio)	*p*-Value*	Odds ratio	95%CI**
Incomplete UCLP	7	11	0.703	1.82	0.66–5.05
Complete UCLP	22	66		0.76	0.38–1.54
Incomplete BCLP	4	7		1.57	0.44–5.65
Complete BCLP	7	23		0.77	0.30–1.95
Incomplete and complete BCLP	3	7		1.15	0.28–4.65

* Chi-squared test.
** Confidence interval.

Table 3-4
Distributions of complete and incomplete cleft types in familial and sporadic Ns CLO, CLA and CLP.

	FNsCL/P *n*(ratio)	SNsCL/P *n*(ratio)	*p*-Value*	Odds ratio	95%CI**
Incomplete (CLO, CLA and CLP)	23	91	0.759	0.89	0.50–1.58
Complete (CLO, CLA and CLP)	38	137		1.05	0.60–1.83
Incomplete and complete (CLO, CLA and CLP)	3	7		1.60	0.40–6.38

* Chi-squared test.
** Confidence interval.

3. Results

Of the total of 425 patients with NsCL/P treated at our department within the 15 years from 1995 to 2010, 82 patients (19.29%) presented a positive history of cleft in their families and 343 patients (80.70%) presented a negative history. The relationships between our analyzed familial patients and their affected family members are summarized in Table 1. First-degree relatives had the highest frequency among the affected relatives of patients with a positive family history.

In the distribution of clefts by type, the frequencies of CLO, CLA, CLP, CPO, were 11%, 18%, 56% and 15% in familial cases, and 13%, 23%, 39% and 25% in sporadic cases, respectively. There was a statistical difference in cleft type using the chi-squared test ($p = 0.038$), odds ratios and 95%CI (OR = 0.84, 0.74, 1.99, 0.52; 95%CI, 0.39–1.79, 0.40–1.36, 1.22–3.24, 0.27–1.01, respectively) (Table 2).