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ORIGINAL ARTICLE

Isolated soft tissue cleft lip: epidemiology and associated dental anomalies

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OBJECTIVES: The aim of this investigation was to study the epidemiology of the isolated soft tissue cleft lip (ICL) population and to evaluate the dental anomalies associated with permanent dentition.

METHODS: The study included 19 children aged 9–13 years presenting ICL selected from 657 cleft lip-affected patients treated during the last 10 years in two craniofacial centers. Only 17 patients could be included for dental anomaly evaluation: Hyperdontia, Hypodontia, Gemination, Talon tooth, Microdontia, and Macrodontia. These were compared with cleft lip and palate (CLP) and cleft lip and alveolus (CLA)-affected populations and with normal populations.

RESULTS: The prevalence of ICL was 2.8%. All types of tooth abnormalities were found to be higher and mainly significant for the cleft side of ICL compared with the normal population. On the side opposite the cleft, the prevalence of dental anomalies reduced toward the normal individuals and was not significantly different. The significant differences found between CLP, CLA, and ICL-affected populations were mostly depicted by lateral incisors and second pre-molar hypodontia.

CONCLUSIONS: Isolated cleft lip is a rare phenomenon among the spectrum of the cleft-affected population. The prevalence of the dental anomalies in ICL maintains the proportional trend according to clefting severity.

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Keywords: cleft lip; epidemiology; dental anomalies; hypodontia; hyperdontia; microdontia; macrodontia; lateral incisor; second premolar; gemination; Talon tooth

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Introduction

The occurrence of dental anomalies, associated with various expressions of cleft lip with or without cleft palate (CP) and alveolar ridge, has long been noted. The literature on this subject was summarized long ago by Jordan, Kraus, and Neptune (Jordan *et al*, 1966). These dental anomalies have been most commonly studied along the years in the combined population of different cleft types that involve soft and/or hard tissues. Interestingly, these anomalies are proportionately higher as the severity of the cleft increases (Boehn, 1963; Ranta, 1972). However, the reports concerning the specific isolated soft tissue cleft lip (ICL)-affected population are relatively limited and the description of the associated dental development is very rare.

The human face and the upper jaw begin their development in the fourth week of gestation by mesenchymal migration and fusion of the primitive facial elements: the paired medial nasal processes and maxillary processes. As the medial nasal processes fuse with each other, they form the anterior portion of the upper jaw – the pre-maxilla - from which the dental incisors originate, and also the medial portion of the upper lip (philtrum) and the primary palate. An ICL is caused by a disturbance in the approximation, fusion or mesenchyme penetration through the epithelial membrane surrounding the medial, and lateral nasal processes and the maxillary process (Goose and Appleton, 1982; Sparber, 1989; Turvey *et al*, 1996).

The clinical term cleft lip is often used in the literature to describe both ICL (Figure 1) and cleft of the lip and the alveolar process (CLA) (Figure 2); both originate in the embryonic formation of the primary palate. However, the two are significantly different from one another from a clinical point of view. Unlike ICL, the osseous cleft of the alveolar process usually requires an autogenously particulate cancellous osseous graft procedure to promote the eruption of permanent lateral incisors (LIs) or cuspids.

The upper LI is unique in terms of variations and abnormalities in humans. In cleft lip and palate-affected

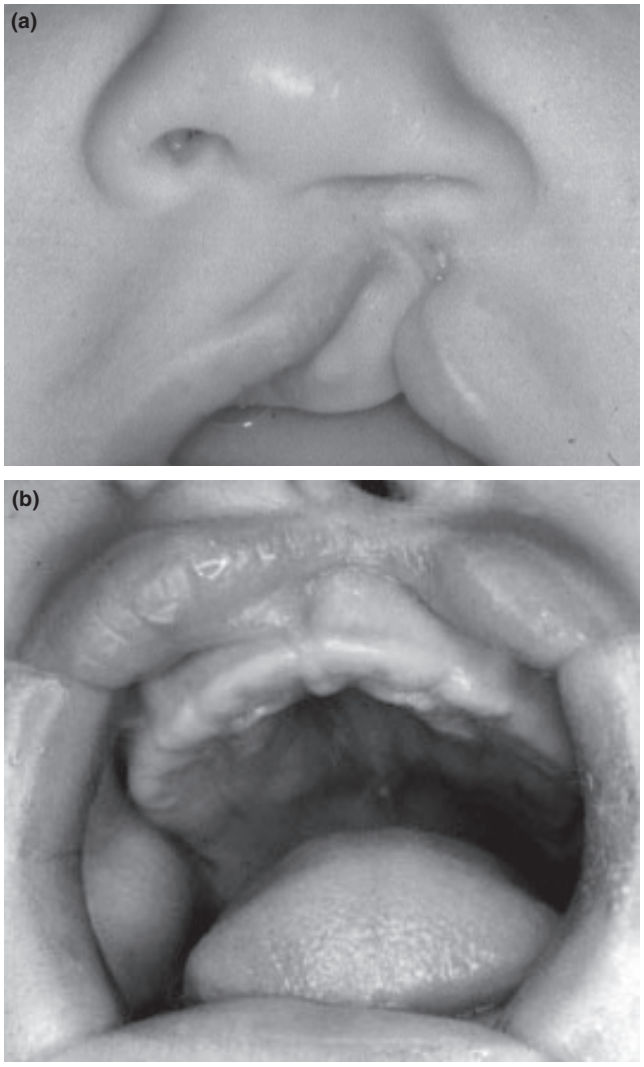

Figure 1 Isolated soft tissue cleft lip. (**a**) Extraoral view. (**b**) Intraoral view – intact alveolar ridge

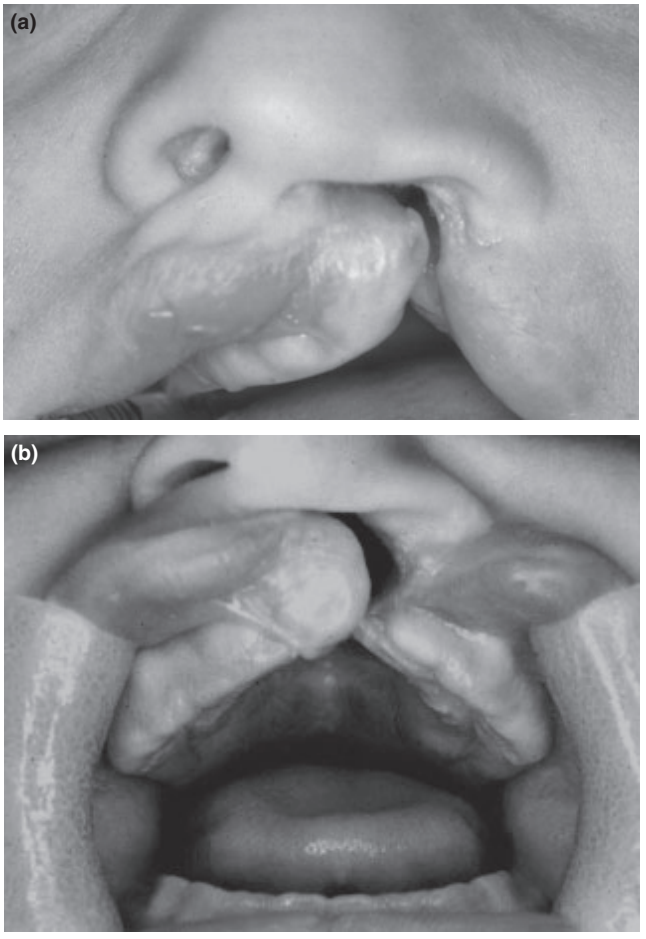

Figure 2 Cleft lip and alveolar ridge. (**a**) Extraoral view. (**b**) Intraoral view – cleft of alveolar ridge extended to the incisive foramen

patients (CLP), the upper LI is the dental structure most vulnerable to injury in the region of the cleft in both deciduous and permanent dentitions (Ranta, 1986). The LI is derived from the dental lamina located immediately lateral to the fusion area between the medial nasal and maxillary processes. The medial nasal and maxillary process fusion area may be anterior (medial) to the LI or cross the medial one-third or the middle of the LI tooth bud position (Ooe, 1957; Ferenczy, 1958; Lisson and Kjaer, 1997). The effects of these embryonic failures are clinically manifested through the LI developmental appearance both in number and size: missing, supernumerary, hypoplastic, dysmorphic, and impacted teeth (Boehn, 1963; Jordan *et al*, 1966; Kraus *et al*, 1966; Ranta, 1986; Semb and Schwartz, 1997). Missing LI in the cleft-affected population appears to range between 10% and 20% for primary dentition, and 30% to 50% for permanent dentition (Bohn, 1950; Boehn, 1963; Jordan *et al*, 1966; Ranta, 1972, 1986, 1990; Ross and Johnston, 1972; Suzuki *et al*, 1992). When the LI is present, it may appear on either side of the cleft in near-normal form or may be rudimentary or malformed, especially in cases where supernumerary teeth are present on both sides of the cleft (Bohn, 1950; Boehn, 1963; Ross and Johnston, 1972). In non-cleft-affected patients, the permanent upper LI is the third most common congenital missing tooth, second to the third molars, and the mandibular second pre-molar (2 PM). This permanent incisor is the most commonly found microdontia (small tooth, peg lateral) with a prevalence of 0.8–8.4% of the population (Neville *et al*, 1995). Additionally, structural anomalies, such as dens invaginatus (dens in dente), most frequently involve the upper LI among the permanent teeth (0.04–10% of all patients). It appears that the tooth buds of both deciduous and permanent maxillary LIs are located in an area that is susceptible to insult during development. Reports in the literature have described that even a small fissure, microform cleft, can be associated with disturbances in the adjacent dental and osseous tissues (Cosman and Crikelair, 1966; Heckler *et al*, 1979).

Hypodontia outside the cleft region has a higher prevalence in cleft-affected children than in others (Boehn, 1963; Ranta, 1972, 1986). The frequency of missing teeth outside the cleft site for children affected

with cleft lip and palate, in descending order of magnitude, is between 7.5% and 32.3% for the maxillary 2 PM, 3.1–10.4% for the maxillary LIs, and 0.4–10.8% for the mandibular 2 PM (Ranta, 1986). Furthermore, a greater delay in dental development has been found in CLP-affected children associated with a higher number of missing teeth compared with their non-CLP-affected counterparts (Dahl, 1970).

As mentioned, ICL-affected patients differ in comparison to CLP-affected patients, in reference to the amount of developmental anomalies of the hard and the soft tissue (Dahl, 1970; Friede *et al*, 1986). Nevertheless, only a limited number of reports have described the dental anomalies that appear in the specific ICL-affected population (Ooe, 1957; Ferenczy, 1958; Shapira *et al*, 2000; Hansen and Mehdinia, 2002). In these studies the authors claim that dental anomalies associated with cleft lip are more frequent than in the general population.

The purpose of this investigation was to study the epidemiology of the isolated soft tissue in the cleft lip-affected population and to evaluate and define the dental anomalies associated with permanent dentition. These dental findings were compared with those found in the complete cleft lip and palate-affected population, in the cleft lip and alveolar ridge-affected population and in the normal population.

Materials and methods

Subjects

The files of 657 cleft patients treated at two Israeli centers, accumulated over the past 10 years were retrospectively scanned. These centers, the Department of Orthodontics of the Hebrew University – Hadassah, School of Dental Medicine in Jerusalem and the Orthodontic and Craniofacial Center of the Rambam Health Care Campus and Technion – Faculty of Medicine - in Haifa, are characterized by cleft-affected populations that are equivalent in their diversity with reference to racial, ethnic, and socioeconomic background. The diagnosis of ICL (a cleft extending through the upper lip partially or completely up to the base of the nostril, but not through the alveolar ridge) (Figure 1) was verified from the patients' charts (i.e. from clinical examinations performed during infancy and childhood). The inclusion criteria, apart from the verified diagnosis, were boys and girls who present: (i) Availability of high quality records including intraoral and facial photos and panoramic and cephalometric radiographs. (ii) Availability of a set of plaster study models of the case. (iii) No evidence of any kind of osseous cleft in the alveolar and/or the palatal bone on the cleft lip side or on the opposite side (i.e. microform, notching or enlarged osseous cleft) as depicted in the orthodontic records.

Exclusion criteria were evidence of a syndromatic condition or visceral anomalies. A total of 19 patients from both centers were diagnosed with ICL, and were classified according to gender and age (Table 1) and according to the cleft site as a unilateral (right or left) or a bilateral cleft lip (Table 2). Two patients did not have the complete required set of high quality records and therefore could not be included in the study. Thus, the final study group for the dental anomaly evaluation included 17 patients (4 patients from the Jerusalem Center and 13 from the Haifa Center).

The data of this population was compared with previous published epidemiologic data and dental norms of the CLP (Vichi and Franchi, 1995; Shapira *et al*, 2000; Aizenbud *et al*, 2005; Tortora *et al*, 2008), CLA (Galie *et al*, 2009)-affected populations and of the general population (Stewart and Prescot, 1976; Brook, 1984; Ranta, 1986; Vichi and Franchi, 1995; Brook *et al*, 1997; Shapira *et al*, 2000; Aizenbud *et al*, 2005).

Table 1 Distribution of the isolated cleft lip-affected study group according to gender and age

Gender	*Boys*	*Girls*	*Total*
N	9	10	19
Mean age (years)	10.17	10.65	10.4
SD age (years)	2.15	2.35	2.17
Max. age (years)	13	13	13
Min. age (years)	9.5	9	9

Table 2 Distribution of the ICL-affected study group according to the cleft side compared with the CLA and CLP-affected population

Cleft site	*Left side*	*Right side*	*Bilateral*	*Total*
N – cleft lip site (ICL)	10	7	2	19
% cleft lip site (ICL)	52.6	36.8	10.6	100
% cleft site of CLP[a–f]	57	33	10	100
Statistical significance between ICL&CLP		$P = 0.926$		
% cleft lip site of CLA[g]	70	30	0	100
Statistical significance between ICL&CLA		$P < 0.0001$		

ICL, isolated cleft lip; CLA, cleft lip and alveolus; CLP, cleft lip and palate.
[a]Dahllof *et al*. (1989).
[b]Harris and Hullings (1990).
[c]Laatikainen and Ranta (1996).
[d]Ranta (1986).
[e]Vichi and Franchi (1996).
[f]Werner and Harris (1989).
[g]Galie *et al*. (2009).

Methods

Panoramic radiographs, photographic intraoral images, and plaster models were used to examine the following dental malformations in the permanent dentition:

Hyperdontia (Supernumerary teeth): defined as the presence of an additional tooth to the normal series, found in any region of the dental arch.

Hypodontia (Tooth agenesis): defined as the existence of at least one developmentally missing tooth. Late development of the 2 PM tooth bud is known (usually in the mandible) to occur among cleft and non-cleft-affected individuals and thus may radiographically appear only after the age of 10 years. In our study, we

considered any case in which a maxillary 2 PM tooth bud could not be detected as tooth agenesis on the panoramic radiograph at the time of the analysis.

Gemination: defined as incomplete development of two teeth from one enamel organ.

Talon tooth: defined as a developmental anomaly characterized by the presence of an accessory cusp-like structure projecting from the cingulum area or cemento-enamel junction of the maxillary or mandibular anterior teeth in both the primary and permanent dentition.

Microdontia and Macrodontia: defined as the presence of one or more teeth smaller or larger than those considered within the normal range; that is, those outside the normal boundaries of variation. For practical purposes this was 1 mm smaller or larger than the antimere, or the mean dimension of the tooth according to Moorrees (1959).

The plaster models were evaluated and measured for the assessment of the LI tooth size. The measurements were taken by using the Nesco 6″digital caliper (Nesco/American Harvest, Two Rivers, WI, USA) for each erupted permanent maxillary LI. The size of the incisors were measured on the cleft lip side and compared with the opposite side.

Statistical methods

The arithmetic mean and standard deviation as well as the chi-square test were calculated. The distribution according to the side of the ICL in the study group was compared with that of the CLA and CLP-affected populations by the use of the chi-square test. The prevalence of the different dental anomalies found in the study was compared with the general population and with the osseous cleft-affected population (CLA and CLP) using a Binomial test. One tail probabilities were calculated and $P < 0.05$ was considered statistically significant. Computations were performed with SPSS software, version 15.0.1 (SPSS Inc., Chicago. IL, USA).

Results

Of 657 cleft cases treated at the two main cleft centers in Israel during the last 10 years, 19 (2.8%) patients with an ICL were selected. Their age and gender distribution is presented in Table 1. Table 2 depicts the prevalence of the ICL-affected population according to the affected side. We did not find any statistically significant differences when comparing these results with the distribution of the CLA (Galie *et al*, 2009) and the CLP (Ranta, 1986; Dahllof *et al*, 1989; Werner and Harris, 1989; Harris and Hullings, 1990; Laatikainen and Ranta, 1996; Vichi and Franchi, 1996), according to the sides of the cleft.

The complete required set of records needed to evaluate dental anomalies were available for 17 cases (2.3%) and consequently they were selected for the dental study and classified as the ICL-affected study group. Table 3 presents the prevalence of dental anomalies found in the ICL-affected study group, compared with the osseous types of cleft-affected populations (CLA and CLP) and to the normal population.

Hypodontia

Three cases of the study group presented with missing LI; two on the cleft side (11.8%) and one on the opposite side (5.9%). Only the prevalence of hypodontia on the side of the cleft was found to be significantly higher than its prevalence among the general population (2.11%) (Brook, 1984; Ranta, 1986; Shapira *et al*, 2000) ($P = 0.049$). However, this phenomenon is very common in the CLP-affected population (74%) (Shapira *et al*, 2000) and when compared with ICL-affected patients, the prevalence is significantly higher ($P < 0.0001$).

Hyperdontia

The prevalence of supernumerary LI was found to be statistically significantly higher on the side of the cleft in ICL-affected patients (29.5%) compared with the general population (2.1%) (Brook, 1974) and the CLP-affected population (11%) (Vichi and Franchi, 1995) ($P < 0.0001$). Lateral incisor hyperdontia was not found on the opposite side of the osseous cleft in the osseous cleft-affected population (Vichi and Franchi, 1995) and therefore a comparison with our study findings (ICL) revealed a statistically significant difference ($P < 0.001$).

Microdontia

Microdontia was found in six cases: five on the cleft side (29.5%) and one on the opposite side (5.9%). Compared with its prevalence among the general population (2.5%) (Brook, 1984), our findings indicate a statistically significantly higher prevalence only on the side of the cleft in ICL-affected patients ($P < 0.0001$). However, when compared with the CLP-affected population, no significant difference was found.

Macrodontia

Two cases (11.8%) demonstrated macrodontia in ICL-affected patients on the side of the cleft. Its prevalence in this group was statistically significantly higher ($P = 0.015$) compared with the general population (1.1%) (Brook, 1984) and to the cleft side in CLP-affected patients (0%) (Rawashdeh and Bakir, 2007; Akcam *et al*, 2008) ($P < 0.001$).

Maxillary 2 PM hypodontia

Comparing the prevalence of 2 PM hypodontia, we found one case of a missing tooth on the ICL side (5.9%), which is higher than the value reported in the general population, i.e. 1.87% (1.3–3.4% in several studies) (Grahen and Lindahl, 1961; Glenn, 1964; Symons *et al*, 1993), and lower than that of the osseous cleft-affected population which is 10.8% (Vichi and Franchi, 1995). No statistically significant difference was found between any of the groups.

Maxillary 2 PM hyperdontia

Hyperdontia of 2 PM was found only in one case (5.9%) on the side of the cleft in the ICL-affected population. Its prevalence in the general population ranges between less than 0.1% and 1% (Glenn, 1964; Salcido-Garcia *et al*, 2004; Berrocal *et al*, 2007) and has not been

Table 3 The prevalence of dental anomalies found in the ICL study group, the osseous types of cleft-affected populations (CLA and CLP) and in the normal population

	Hypodontia		*Hyperdontia*		*Microdontia*		*Macrodontia*		*2 PM Hypodontia*		*2 PM Hyperdontia*		*Form and development anomalies*	
	Cleft side	*Opposite side*	*Cleft side*	*Opposite side*	*Cleft side*	*Opposite side*	*Cleft side*	*Opposite side*	*Cleft side*	*Opposite side*	*Cleft side*	*Opposite side*	*Gemination*	*Talon tooth*
N	2	1	5	2	5	1	2	0	1	0	1	0	2	1
%	11.8	5.9	29.5	11.8	29.5	5.9	11.8	0	5.9	0	5.9	0	11.8	5.9
Number of the general population[b–d]	451/21 384		23/1115		27/1115		12/1115		399/21 384		5/2241		11/2241	–[a]
% of the general population[b–d]	2.11		2.1		2.5		1.1		1.87		0.2		0.5	2
Statistical significance between ICL and general population	$P = 0.049$	non-sig	$P < 0.0001$	non-sig	$P < 0.0001$	non-sig	$P = 0.015$	non-sig	non-sig	non-sig	$P = 0.003$	non-sig	$P = 0.003$	non-sig
Number of CLP-affected patients	205/278	10/119	11/77	0/77	20/77	4/77	0/77	1/77	4/87	1/87	0/116	0/116	No data	No data
% in CLP-affected patients[e–h]	74	8.4	14.2	0	26	5.1	0	1.3	4.9	1.3	0	0	No data	No data
Statistical significance between ICL and CLP	$P < 0.0001$	non-sig	non-sig	$P < 0.001$	non-sig	non-sig	$P < 0.001$	non-sig	non-sig	non-sig	$P < 0.002$	non-sig		
Number of CLA-affected patients[j]	5/20	2/20	No data	No data	No data	No data	No data	No data	4/20	2/20	No data	No data	No data	No data
% in CLA-affected patients[j]	25	10	No data	No data	No data	No data	No data	No data	20	10	No data	No data	No data	No data
Statistical significance between ICL and CLA	non-sig	non-sig							non-sig	non-sig				

ICL, isolated cleft lip; CLA, cleft lip and alveolus, CLP, cleft lip and palate, non-sig, statistically not significant.
[a]Average percent of different reported cases because of a marked difference in the prevalence values.
[b]Brook (1974).
[c]Eidelman *et al*. (1973).
[d]Salcido-Garcia *et al*. (2004).
[e]Sedano *et al*. (1989).
[f]Aizenbud *et al*. (2005).
[g]Shapira *et al*. (2000).
[h]Tortora *et al*. (2008).
[i]Vichi and Franchi (1995).
[j]Galie *et al*. (2009).

reported in CLP-affected patients. The difference between the groups was found to be statistically significant ($P \leq 0.003$).

Additional tooth anomalies

Other tooth anomalies were also diagnosed in ICL-affected patients in this study and were compared with the general population, i.e. Gemination and Talon tooth. The only statistically significant difference that was found, appeared in the prevalence of LI gemination in the non-cleft side of the ICL-affected population (11.8%) compared with the general population (0.1–1%.) (Brattstrom and McWilliam, 1989; Salcido-Garcia *et al*, 2004; Berrocal *et al*, 2007; Lai *et al*, 2008) ($P = 0.003$).

Discussion

Clefting of the lip and palate is one of the most frequent congenital malformations. The incidence of CLP varies in different populations: 1:500 births in the Asian population, 1:1100 births in the Caucasian population and 1:2500 births in the African population (Archer, 1966). Epidemiology of clefts in many studies is of limited value when all orofacial cleft types are combined without distinction between ICL, CLA, CLP and CP. As these types are considered variations of the same developmental anomaly, their prevalence should be recorded separately (Turvey *et al*, 1996). Several authors have presented data regarding cleft lip-affected patients but their publications did not specify the exact definition and inclusive criteria for these patients (Chow, 1994; Vallino-Napoli *et al*, 2004). Whether their study groups included ICL-affected patients or cleft lip-affected patients which also present alveolar bone involvement up to the incisive foramen (known as CLA) is usually unclear.

In this study the identification of ICL was precise and meticulous. Other cleft types involving osseous tissue (i.e. CLP, CP, and CLA) were not included in the study. Furthermore, the ICL-affected patients' files that accumulated at two orthodontic department archives were limited to the treatment of cleft patients and craniofacial defects. In many cases, ICL-affected patients underwent surgery at a young age, i.e. 3–6 months old for lip closure and did not suffer any other dental or osseous pathology. Therefore, many of these cleft type patients (i.e. ICL) did not require any other surgical and/or orthodontic treatment and consequently were not assigned to these orthodontic clinics. This may explain the scarcity of ICL files among cleft-affected patients treated at these centers (only 2.8%).

Isolated soft tissue cleft lip without evidence of any kind of osseous involvement is a relatively rare phenomenon (Hansen and Mehdinia, 2002; Galie *et al*, 2009). Shapira *et al* (Shapira *et al*, 1999) reported a prevalence rate of 2.1%, equally distributed between male and female patients, quite similar to the one we found in our study (2.8%). These findings contradict the findings of many studies which have emphasized sex dimorphism in orofacial clefts, where CLP occurs more frequently in male and CP occurs most often in female patients (Chow, 1994; Vallino-Napoli *et al*, 2004; Aizenbud *et al*, 2005; Lai *et al*, 2008). This contradiction may account for the attenuated form of cleft morphology as depicted in ICL i.e. ICL is not severe enough to be expressed by sex dimorphism as in CLP and CP. Therefore, probably, no sex pre-dominance is expected when dividing the cleft lip phenotypes into finer subcategories. However, our results, which resemble Shapira's (Shapira *et al*, 1999) findings, were characterized by a small study group sample of ICL. A larger sample of ICL phenotype might be obtained by a multicenter epidemiologic study, which could clarify the assumption that gender pre-dilections are proportionately higher as clefting severity increases. Many studies have presented left side pre-dominance for the cleft anomaly (Bishara and Iversen, 1974; Goose and Appleton, 1982; Athanasiou *et al*, 1987; Normando *et al*, 1992; Chow, 1994; Vallino-Napoli *et al*, 2004). Our findings support this assumption for the ICL-affected population. Galie *et al* (Galie *et al*, 2009) revealed similar percentages in his recent report on 20 CLA-affected Romanian children; however, the gender distribution in his study was different, with female pre-dominance (12:8).

Cleft lip and palate and teeth anomalies

The congenital lack of one or more permanent teeth is the most common congenital anomaly found in humans, affecting about 20% of the population worldwide (Goose and Appleton, 1982). Oral clefts in humans are often associated with delayed development of dentition and anomalies of the number, size, and shape of teeth both on the cleft and non-cleft sides (Sparber, 1989; Turvey *et al*, 1996). Rawashdeh and Bakir (Rawashdeh and Bakir, 2007) showed in their study that tooth size reduction occurred across all permanent tooth types and among early and late-forming teeth in cleft-affected patients compared with controls. Akcam *et al* (Akcam *et al*, 2008) reported that the mesio-distal, labio-lingual, and occluso-gingival dimensions of teeth were generally smaller in CLP-affected subjects than in Class I subjects. Similarly, Hellquist *et al* (Hellquist *et al*, 1979) in his group of 172 children suffering from cleft lip, with or without CP, found that only 6.2% presented with teeth of normal size and shape. In another study, all patients were found to have some degree of deformity of the anterior teeth in the area of the cleft (Olin, 1964).

It is generally accepted that agenesis of teeth is related to an overall reduction in tooth size. Consequently, hypodontia and microdontia tend to occur in the same children (Boehn, 1963; Jordan *et al*, 1966; Kraus *et al*, 1966; Ranta, 1972; Turvey *et al*, 1996). The reason for the high prevalence of anomalies is not fully understood, but the assumption is that the etiology is a pre-natal insult that interacts with a poorly buffered genotype (Graber, 1978). Hypodontia is, to a great degree, genetically determined and transmitted by autosomal dominant inheritance, with incomplete penetrance and variable expression (Grahnen, 1956; Burzynski and Escobar, 1983). A mutation in *MSX1* and *IRF6* genes has been suggested as a factor causing common dental

developmental anomalies (Vastardis *et al*, 1996). Environmental factors, however, may also play a role in the etiology of this condition (Boruchov and Green, 1971; Gravely and Johnson, 1971).

Orofacial clefts are also multifactorial and a variety of environmental factors such as maternal smoking, maternal ingestion of anticonvulsants or pesticides, have been implicated (Sparber, 1989; Turvey *et al*, 1996). Interestingly, the same genes, *MSX1* and *IRF6* (both of which encode transcription factors), as well as *FGFR1* (which encodes a growth factor receptor) are important in palate formation. Therefore, a mutation in those genes may result in the occurrence of CP and lip and different dental anomalies (Vastardis *et al*, 1996). A future study is warranted to investigate whether the genetic factors involved in the clefting phenomenon influence the risk of having dental anomalies. It would be reasonable to assume that genes such as those mentioned above might act as potential confounders as well as pre-disposing factors. Therefore, their stratification should be preformed, or its presence should be evaluated in a study of patients manifesting hypodontia only, without any type of cleft. The increased incidence of hypodontia in children with clefts might be a result not only of the genetic factors directly affecting hypodontia but also of the factors causing the cleft itself (Ranta and Rintala, 1983; Ranta *et al*, 1983). This suggests that the same etiologic factors may be responsible for both the formation of clefts and hypodontia in the affected children (Bailit *et al*, 1968).

ICL and teeth anomalies

To our knowledge, the present study is the first to report on the dental anomalies characterized in ICL-affected patients without any overt osseous involvement in the cleft pathology. Most of the studies report these anomalies in CP, complete CLP, incomplete CLP and submucous CP-affected patients. An explanation for this may be the scarcity of the ICL phenomenon compared with other types of orofacial cleft. The data obtained from our study helps to position the ICL-affected population on this cleft severity continuum with a significant difference from both the normal and osseous cleft-affected populations. The most common dental anomaly for the cleft-affected population – LI hypodontia – clearly positions the ICL-affected population as a hybrid between the normal population and the osseous cleft-affected population (CLP & CLA) as depicted in Figure 3. Furthermore, the gender distribution of our ICL-affected patients, which is with equal prevalence among male and female patients, corroborates this evidence as sex dimorphism for the osseous cleft-affected population was not recorded (Chow, 1994; Vallino-Napoli *et al*, 2004; Aizenbud *et al*, 2005; Lai *et al*, 2008). The 2 PM hypodontia prevalence maintains this segregation trend, although the differences are not statistically significant (Figure 3). The value for 2 PM hypodontia in the CLA population is exceptionally higher (although not significant). This may be explained by the small sample of the study (four cases of missing 2 PM in 20 patients) (Galie *et al*, 2009). These findings support the previous studies where the dental anomalies were found in proportionately higher prevalence as clefting severity increased (Boehn, 1963; Haataja *et al*, 1971; Petrovic, 1973; Zilberman, 1973; Ranta, 1984; Ranta and Tulensalo, 1988; Lopes *et al*, 1991; Vichi and Franchi, 1995; Dewinter *et al*, 2003). The reason for this difference is probably the mesenchymal tissue deficiency, which is the largest in clefts involving osseous tissue (Archer, 1966). Consequently, the risk of dental anomalies, namely a missing LI, is the highest in these clefts.

The least severe type of cleft on this continuum may be the minimal cleft lip (microform), which is the mildest form of cleft. This type of cleft may also present dental defects, alveolar arch discontinuity, and nasal deformity (Cosman and Crikelair, 1966); however, no literature on the prevalence of dental anomalies in these cases is available.

When reviewing the achieved results for the non-cleft side, the clear continuum based on cleft severity disappears (Figure 4). A missing LI or other malformations on the non-cleft side may be viewed as a microform, that is to say, a minimal way of expressing the injury to the normal embryonic tissue development; an injury that is not severe enough to cause a full cleft. (Archer, 1966) Therefore, the clear and significant segregation between cleft types reflected by dental anomalies on the cleft side cannot be expressed by a microform of the non-cleft side.

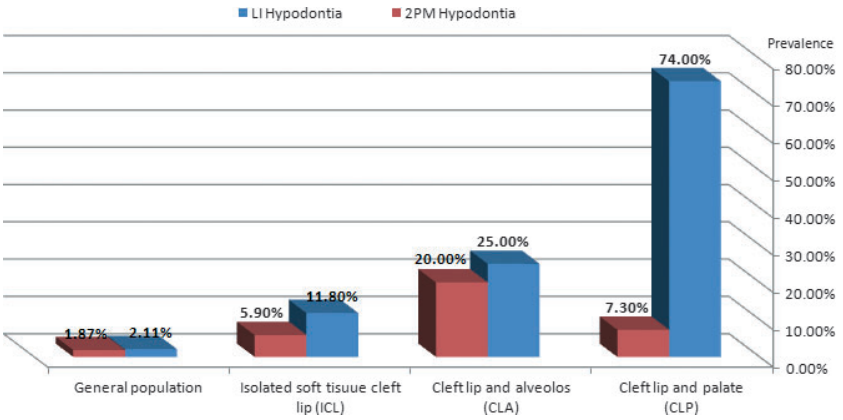

Figure 3 Comparison of maxillary lateral incisor and 2 PM hypodontia prevalence among the normal, isolated cleft lip, cleft lip and alveolus, and cleft lip and palate-affected populations

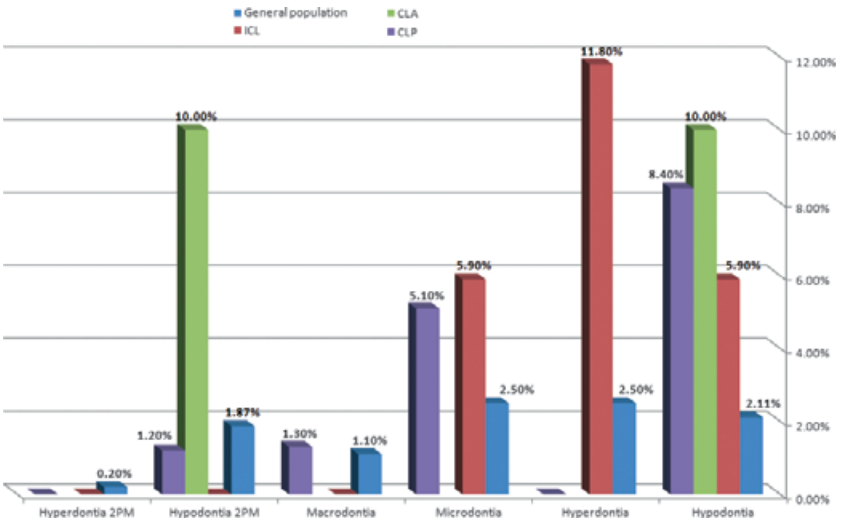

Figure 4 Prevalence of dental anomalies in the non-cleft side of the cleft lip and palate, cleft lip and alveolus, and isolated cleft lip-affected population and the normal population

Figure 5 demonstrates the prevalence of microdontia, macrodontia and LI and 2 PM hyperdontia in the ICL-affected population. These values were found to be higher in ICL compared with the normal and CLP-affected populations. The reason for this probably lies in the fact that clefts involving osseous tissue present with large amounts of mesenchymal tissue deficiency. Thus, it is easier for them to develop into hypodontia cases rather than hyperdontia, microdontia, or macrodontia cases. In ICL the tissue deficiency is smaller, resulting in a higher prevalence of LI crown malformations such as microdontia or macrodontia as well as hyperdontia anomalies than of hypodontia, caused by the splitting of the tooth bud (which may be caused by the cleft itself). This trend supports the tendencies reported by Nagai, (Nagai *et al*, 1965) Berkowitz (Berkowitz, 1978) and Hansen, (Hansen and Mehdinia, 2002) who also found a high prevalence of supernumerary maxillary LIs in ICL cases. This association of ICL with perturbations in dental development is therefore not only caused by genetic factors but also by environmental factors such as local space. This explanation actually strengthens the continuum theory based on cleft severity. As ICL is an attenuated cleft form, it involves less mesenchymal tissue enabling higher incidences of LI crown malformation and L1 supernumerary reflected in sufficient tissue space for dichotomic tooth bud development. An ICL is caused by a disturbance in the mesenchymal fusion of the medial and lateral nasal processes with the maxillary process. The tooth formation process involves a 'signal' from the dental lamina to the mesenchymal tissue around it (called the dental papilla), as well, and this mesenchymal tissue turns into the pulp-dentin complex, which is the main dental tissue subject to pathological influences (Ranta, 1986). For all of these reasons, it can be concluded that the factors which cause the cleft itself may have additional effects and may increase the risk of hypodontia and other dental malformations on the cleft side and on areas distant from the side of the cleft. Therefore, tooth anomalies are expected in the ICL-affected population even if osseous tissue is not involved.

Our results support this assumption as the prevalence of almost all the types of tooth anomalies (LI hypodontia and hyperdontia, 2 PM hypodontia and hyperdontia, LI microdontia and macrodontia, gemination, and

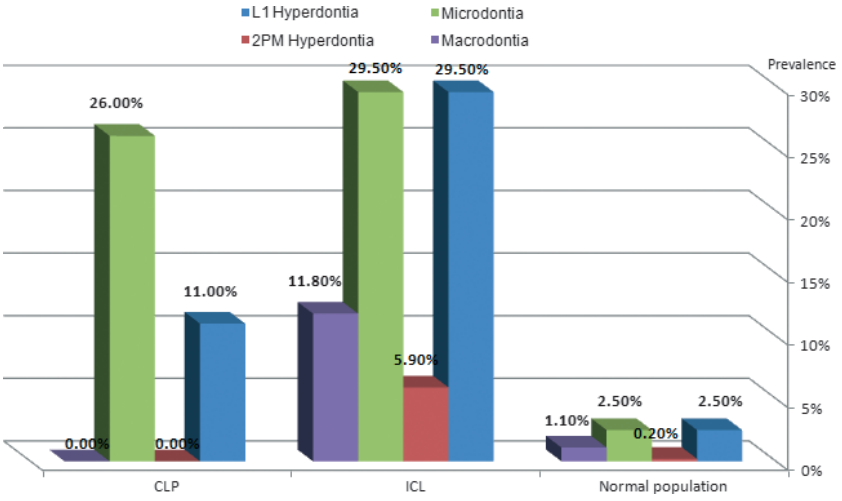

Figure 5 Highest prevalence of dental anomalies on the cleft side by type recorded for the isolated cleft lip-affected population, compared with the cleft lip and palate-affected population and the normal population

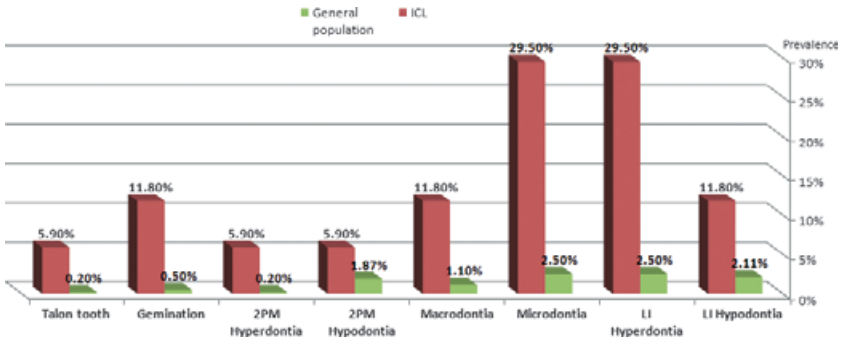

Figure 6 The prevalence of dental anomalies were found to be higher in the isolated cleft lip-affected population on the cleft side compared with the normal population

Talon tooth) was evaluated in this study and found to be higher and for most, even significantly higher for the cleft area of the ICL-affected population compared with the normal population (Table 3, Figure 6). If we look at the side opposite the cleft, the prevalence of these dental anomalies reduced toward the normal population sometimes even a bit higher or slightly lower, yet not significantly different. Interestingly, these ICL prevalence values for the side opposite the cleft were found to resemble the prevalence in the non-cleft side of the osseous cleft-affected population i.e. CLA and CLP (Figure 4).

Conclusions

In conclusion, the results of this study suggest that the considerably rare ICL is not just typified by a single anatomically localized disruption in the development of the soft tissue lip. These patients are characterized by a higher rate of dental anomalies on the cleft side compared with the normal population and the osseous cleft-affected population. The most significant phenomenon of dental anomalies is LI hypodontia which clearly positions the ICL-affected population as a hybrid between the normal and the osseous cleft-affected populations on the cleft severity continuum scale. The prevalence of several other dental anomalies such as microdontia, macrodontia, and hyperdontia, which require the expression of mesenchymal tissue space, is specifically higher in this attenuated cleft type. Therefore, the association of ICL with different kinds of perturbations in dental development is caused not only by genetic factors but also by local factors such as tissue space. A multicenter study is warranted to collect a large enough sample to verify this ICL phenomenon.

A CP team should take these results under consideration during consultation on cases of ICL in newborn and children concerning the expected dental manifestations and future orthodontic treatment that will be required.

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