# Registries of cleft lip/palate cases between 2004 and 2010 in Denizli, Turkey

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**ABSTRACT.** Oral clefts are one of the most common birth defects in humans. However, few population-based studies of these defects have been carried out in Turkey. Our objective was to determine the registries of cases of cleft lip and palate. All cases of cleft lip and palate referred to central state hospitals in Denizli between January 2000 and May 2010 were investigated retrospectively. Anomalies were determined and classified according to the ICD-10 coding system. A total of 194 cases were identified consisting of 92 females (47.4%), 100 males (51.6%), and 2 subjects of undetermined gender (1%) with an age range of 1 to 65 years. Among the 194 cases, 127 subjects (65.5%) had isolated cleft palate, including 63 females and 64 males; 42 (21.6%) subjects had cleft lip, including 17 females and 25 males;

and 25 subjects (12.9%) had cleft lip and palate, including 12 females and 13 males. Studies of oral cleft prevalence are insufficient in Turkey owing to the incompleteness of registries, and the chromosome analysis rate has reached a reasonable level only in recent years.

**Key words:** Cleft lip; Cleft palate; Registry-based cases; Turkey; Folic acid; Nonsyndromic

## INTRODUCTION

Nonsyndromic (95% of cases) cleft lip (CL) with or without cleft palate (CL/P), MIM119530, is a frequent congenital malformation of the orofacial region. Clefts can compromise respiration, swallowing, speech, articulation, and hearing and frequently demand costly multiple surgical procedures and medical interventions (Hsieh et al., 2007). Although treatable, children with CL/P and their families are at risk of developing psychopathology, especially seasonal affective disorder and major depressive disorder (Demir et al., 2011). Children affected by CL/P need multidisciplinary care from birth to adulthood, and they show increased morbidity and mortality during their lifetimes compared with that in the general population. Cancer risk is also elevated in individuals with CL/P and their first three-degree relatives (Vieira et al., 2012). CL/P is classified according to the degree of deformity, and the classification of Vaeau (1931) is widely accepted. In many regions of the world, CL/P is more common than Down syndrome, constituting 65% of all congenital abnormalities (Gorlin et al., 2001).

Every two minutes, a child with CLP is born in the world, which translates to 660 children daily; 235,000 new cases of fissures are seen annually. With the growth of the world population, 3200 new CL/P cases per year can be expected (Kot and Kruk-Jeromini, 2007). Recurrence risk of nonsyndromic CL/P has been evaluated in 4 to 10% of cases (Stuppia et al., 2011). Interestingly, orofacial clefts (OFC) have become more frequent from north to south and east to west on each continent on the International Database of Craniofacial Anomalies world maps. The rate of racial prevalence is highest in whites, then Hispanics, Asians, and Africans (Hsieh et al., 2007). Internationally, the rate of CL has declined, with an average overall prevalence of 7.94 in 10,000. In Europe, significant differences in prevalence have been found between registries and within countries. Countries with the highest and lowest rates are Japan (19.05) and South Africa (3.13), respectively. In the United States, the national rate averages 7.75, with highest and lowest rates in Maryland (21.46) and West Virginia (2.59), respectively (Loane et al., 2011; Tanaka et al., 2012). Other reported incidences are 1.94 and 1.46 cleft cases per 1000 live birth in the Philippines and Brazil (Martelli-Junior et al., 1998; Murray, 2002). A Polish study has uncovered a particularly interesting heritage result: fathers with CL/P have a 2-fold risk for CL/P in sons, fathers with cleft palate (CP) have a 2-fold risk of having a daughter with CP, mothers with CL/P have a 3-fold of having a son with CL/P, and mothers with CP have a 2-fold risk of having a daughter with CP (Kot and Kruk-Jeromini, 2007).

Several studies on the formation of nonsyndromic oral clefts have failed to determine the exact etiology and pathogenesis; however, CL/P is known to result from the interaction of genetic and environmental factors. Enhanced socioeconomic status decreases the prevalence, as does a diet fortified with folic acid and vitamin supplements. Smoking with certain gene

(*GSST1*) variants, alcohol use, steroids, and anticonvulsants increase the prevalence (Kohli and Kohli, 2012). Living in more rural areas is associated with an increased adjusted risk of CL/P (Messer et al., 2010).

Women who conceive during spring, summer, or autumn have a 2.6-fold increased risk of having a baby with a cleft in Germany but not in Northern Ireland (Krost and Schubert, 2006; Gregg et al., 2008). Isolated CL/P is genetically heterogeneous. Many linkages and associations have been found on various chromosomes (6p24-OFC1, 2p13-OFC2, 19q13-OFC3, 4q-OFC4), and polymorphisms and mutations on some genes (*IRF6*, *FOXE1*, *MSX1/2*, *MTR*, *MTHFR*, *TGFA*, *STAB2*, *CLPM1*, *PVRL1*, and *TBX22*) have been found in family and population studies (Stuppia et al., 2011; Kohli and Kohli, 2012).

The incidence rates of CL/P and isolated CP have been reported as 0.95/1000 and 0.77/1000, respectively, in Turkey (Tunçbilek, 1996). Studies on oral clefts are mainly case presentations in Turkey, and few population data on other conditions are available (Borcbakan, 1969; Tunçbilek, 1996). We were unable to find data from Turkey when we searched international registries and organization such as EUROCAT, WHO, ICFA, and EMLAMC [Latin American Collaborative Study of Congenital Malformations, the oldest existing organization (established in 1967) and WHO appointee since 1989], whereas many countries from Bolivia to Iran regularly report to the WHO. Hence, we concluded that each publication we found in our search was valuable for information about and evaluation of these malformations in Turkey. The objective of this study was to examine and highlight the registries of CL/P in state hospitals of Denizli and identify potential risks for the disorder and guidance for education and genetic consulting.

## MATERIAL AND METHODS

This descriptive and retrospective study on oral clefts was performed in 2 main hospitals (Servergazi and Denizli State Hospitals) in Denizli, Turkey, in which 90% of births occur. Data were collected from records made between January 2004 and September 2010. A total of 194 cases with oral clefts were identified. Cases were retrieved with Q35-37 according to ICD-10 (WHO, 1992). Data were analyzed using SPSS version 10. Descriptive statistics were presented as frequencies and percentages.

## RESULTS

A total of 194 cases consisting of 100 males (51.6%), 92 females (47.4%) and 2 subjects of undetermined gender (1%) with an age range of 1 to 65 years were included. Percent distribution by type of cleft according to gender is given in Table 1. The cases included 127 subjects (65.5%) with CP, including 63 females and 64 males, and 42 subjects (21.6%) with CL, including 17 females and 25 males. A total of 25 subjects (12.9%) had CL/P, including 12 females and 13 males. Most of the patients had been referred to the outpatient clinics of plastic and reconstructive surgery and a small number to the pediatrics and neck surgery departments. The majority of subjects with CL/P were male (51.6%). Most of the patients (61.9%) had been diagnosed within the first 5 years of life. The study group consisted of 29 infants (14.9%), including 9 subjects (46.9%) between the ages of 1 and 5, 21 subjects (11.3%) in puberty and 33 adults (28.2%) older than 20 years (Table 2).

**Table 1.** Distribution of cleft types according to gender.

| Type of cleft | Sub total [N (%)] | ICD-10 code | Gender | | Unknown | Total |
|---|---|---|---|---|---|---|
| | | | Female | Male | | [N (%)] |
| CP | 127 (65.5) | Q35 | 35 | 33 | | 68 (35.1) |
| | | Q35.0 | 4 | 4 | | 8 (4.1) |
| | | Q35.1 | 8 | 4 | 1 | 13 (6.7) |
| | | Q35.2 | 1 | 3 | | 4 (2.1) |
| | | Q35.3 | 0 | 2 | | 2 (1.0) |
| | | Q35.4 | 2 | 3 | | 5 (2.6) |
| | | Q35.5 | 0 | 1 | | 1 (0.5) |
| | | Q35.6 | 1 | 3 | | 4 (2.1) |
| | | Q35.7 | 6 | 1 | | 7 (3.7) |
| | | Q35.8 | 0 | 1 | | 1 (0.5) |
| | | Q35.9 | 6 | 7 | 1 | 14 (7.2) |
| CL | 42 (21.6) | Q36 | 16 | 22 | | 38 (19.6) |
| | | Q36.0 | 0 | 3 | | 3 (1.5) |
| | | Q36.9 | 1 | 0 | | 1 (0.5) |
| CL+P | 25 (12.9) | Q37 | 9 | 13 | | 22 (11.3) |
| | | Q37.5 | 3 | 0 | | 3 (1.5) |
| Total N (%) | 194 (100) | | 92 (47.4) | 100 (51.6) | 2 (1) | 194 (100) |

C = cleft; P = palate; L = lip.

**Table 2.** Distribution of ages.

| Age (years) | N | % |
|---|---|---|
| 1-5 | 120 | 61.9 |
| 6-10 | 20 | 10.3 |
| 11-15 | 9 | 4.6 |
| 16-20 | 13 | 6.7 |
| 21-25 | 10 | 5.2 |
| 26-30 | 5 | 2.6 |
| 31-35 | 6 | 3.1 |
| 36-40 | 6 | 3.1 |
| 41-45 | 1 | 0.5 |
| 46-50 | 2 | 1.0 |
| 51-55 | 0 | 0.0 |
| 56-60 | 1 | 0.5 |
| >61 | 1 | 0.5 |
| Total | 194 | 100.0 |

## DISCUSSION

We fond a total of 194 OFC cases consisting of 127 (65.5%) CP, 42 (21.6%) CL, and 25 (12.9%) CL/P. In contrast to these rates, Altunhan et al. (2012) have recently detected the following in Konya Turkey, Central Anatolia, in 121 babies: 86 (71%) CL/P and 35 (29%) CP. The percentages of CL and CL/P in our study is different form studies in The Netherlands (CL 21, CL/P 46, CP 33%) and Korea (CL 21, CL/P 46, CP 33%), and these malformations are also more common in female Pakistani subjects (CL 42, CP and CL/P 34%) (Cornel et al., 1992; Kim et al., 2002; Elahi et al., 2004).

Pan-European analysis has shown that the prevalence of CP, neural tube defects, and spina bifida are decreasing trends. The rates of decrease are 2% per year for CP and 1.6% for neutral tube defects. However, an increase in CL/P has been reported in Wales (UK) and Zagreb (Croatia). Of particular interest was a decrease in spina bifida in Wales. The inconsistent trend in this anomaly across Europe

requires investigation (EUROCAT Statistical Monitoring Report, 2009; Loane et al., 2011). Therefore, we concluded that the prevalence of various types of clefts might differ between populations.

In regard to genes, in a case-control study of Brazilian families with CL/P, Gaspar et al. (2004) have observed that the *MTHFR* 677T allele is associated with increased risk of malformation. However, Sözen et al. (2009) found no association with *MTHFR* 677T in Venezuelan subjects. Mutation screens of *FOXE1* have identified 2 family specific missense mutations at highly conserved amino acids (Moreno et al., 2009). *WNT3* rs3809857 variant and some haplotypes are associated with a decrease in the risk of nonsyndromic CL/P in Poland, in which the prevalence of CL/P is as high as 15.6 in 10,000 births (Mostowska et al., 2012). Significant epistatic interaction has been observed between *MTHFR* (rs1801133), *MTR* (rs1805087), and *PEMT* (rs4646406) in nonsyndromic CL/P susceptibility in Poland (Mostowska et al., 2006).

In conclusion, a better registry system is needed, as are extensive family or population studies based on genetic analysis. The exact relationship between candidate genes and oral clefts still require elucidation. Identifying specific environmental risks may be possible, allowing woman to avoid exposure to malformation-inducing agents. The contribution of data to an international data bank system must be promoted in all countries because the heterogeneity of geographic and ethnic data is valuable for clarifying CL/P etiology.

## ACKNOWLEDGMENTS

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