Epidemiology of Cleft Lip and Palate among Jews and Bedouins in the Negev

Eldad Silberstein MD[1], Tali Silberstein MD[2], Emil Elhanan MD[1], Eitan Bar-Droma DMD[1], Alexander Bogdanov-Berezovsky MD PHD[1] and Lior Rosenberg MD[1]

[1]Center of R&D in Plastic Surgery and [2]Department of Obstetrics and Gynecology, Soroka University Medical Center and Faculty of Health Sciences, Ben-Gurion University of the Negev, Beer Sheva, Israel

ABSTRACT: **Background:** Clefts of the lip and palate are the most common significant congenital birth anomaly of the orofacial region. The condition may vary from a minor easily correctable cleft to a significant functional and cosmetic incapacitation. This is the first epidemiological study of orofacial clefts in the Negev region in Israel.

Objectives: To establish the frequency of cleft lip and palate in the population of the Negev, characterize the demographic features of affected individuals and find possible risk factors, compare the risk in two major population groups: Bedouin and Jewish in a well-defined geographic area, and determine whether there is a change over time in the birth of babies with facial clefts.

Methods: We conducted a retrospective survey of the Soroka Medical Center archives. The sample population comprised all 131,218 babies born at Soroka during the 11 year period 1 January 1996 to 31 December 2006. Statistical tests used Pearson's chi-square test, Student's *t*-test and Spearman's correlation coefficient test according to the type of parameter tested.

Results: During the study period 140 babies were born with orofacial cleft. The overall incidence of cleft lip and palate was 1.067/1000. The incidence of facial clefts was 1.54/1000 among Bedouins and 0.48/1000 among Jews ($P < 0.001$). Cleft palate was significantly more frequent in female than male babies ($P = 0.002$). Over the study years we found a significant decrease in the incidence of facial clefts in the Bedouin population, with Spearman's correlation coefficient rank -0.9 ($P < 0.01$).

Conclusions: A significant decrease occurred in the incidence of facial clefts among Bedouin. This change may be attributed to prenatal care in the Bedouin Negev population as part of social and health-related behavior changes. The reduction in rates of congenital malformations, however, does not mean a reduction in the number of cases in a growing population. Also, with a modern western lifestyle, the expectancy and demand for reconstructive facial surgery and comprehensive care for these children are on the rise.

IMAJ 2012; 14: 378-381

KEY WORDS: cleft lip, cleft palate, birth defects, congenital anomalies, epidemiology, Negev, Bedouin health

Clefts of the lip and palate are the most common significant congenital birth anomaly of the orofacial region. Its reported incidence is 1/1000 live births in Caucasian populations and up to 3.6/1000 cases in American Indians, or as low as 0.3/1000 in African Americans [1]. The condition may vary from a minor easily correctable cleft to a significant functional and cosmetic disturbance. Even with corrective surgery patients face a lifetime of social and aesthetic challenges. Facial cleft has also been linked to an elevated risk of cancer in later life [2] and an increased overall mortality well into adulthood [3]. Cleft lip and palate may be an isolated anomaly or could be associated with syndromes such as Apert, Crouzon or Down.

Cleft lip with or without cleft palate is considered etiologically distinct from isolated cleft palate. While the first is a manifestation of a disruption of the primary palate situated anterior to the incisive foramen, the latter is a disruption of the secondary palate formation [1]. Cleft lip with cleft palate or without cleft palate is more frequent among male infants, while isolated cleft palate is more frequent among females. Several studies have found that maternal exposure to alcohol, smoking, toxic material and certain drugs may increase the risk for facial cleft in an embryo. In addition, maternal age may contribute to the development of cleft. A family history of cleft lip, cleft lip with cleft palate, or cleft palate, is the strongest relative risk for having a baby born with the anomaly [1].

Halevi [4], in 1967, reported the incidence of facial clefts in Israel to be 0.76/1000 live births. Others have found variable rates, ranging from 0.54/1000 to 1.6/1000 [5-7]. Harlap et al. [7] found differences in the rates between the Jewish and Arab populations in Jerusalem: 3.9/1000 and 1.5/1000 clefts/live births, respectively. However, Jaber and colleagues [8]

found the prevalence of facial clefts in the Arab population of the city Taibe to be 1.56/1000, which is similar to rates in other western communities as well as the Jewish population in Israel. No such epidemiological survey has been done on the population of the Negev, Israel's southern desert region. Soroka University Medical Center is the only medical center for the entire Negev population of more than 500,000 people. The Negev population is estimated to comprise about 75% Jews and 25% Bedouins. It is estimated that most (> 94%) of the Negev-resident mothers deliver their babies at Soroka. This makes it a reliable source for an epidemiological study of congenital anomalies such as facial clefts that can be diagnosed at birth and is an opportunity for comparison between different populations. The aims of this study were: a) to establish the incidence of cleft lip and cleft palate in the population of the Negev, b) to characterize the demographic features of affected individuals and identify risk factors, c) to compare the risk factors in two major population groups – Bedouin and Jewish, and d) to determine whether a change over time occurs in the birth of babies with facial clefts.

PATIENTS AND METHODS

Following approval of the hospital ethical committee we conducted an 11 year retrospective survey of the Soroka Medical Center archives. Residents of the Negev comprised the study population. The sample population included all babies born at Soroka between 1 January 1996 and 31 December 2006. Data were collected from four different sources: a) the main archive of Soroka Medical Center, including details of all children with the diagnosis of a cleft lip and/or palate; b) the OFEK 6® medical record software database; c) ATD Software, which provided baseline details of mothers of the affected children; and d) the Obstetrics and Gynecological division's archive, which provided details on the course of pregnancy as well as information regarding the gender and origin of newborns.

Statistical analysis was performed with Microsoft Office Excel 2003® and SPSS® version 14 software. Statistical tests used Pearson's chi-square test, Studen's *t*-test and Spearman's correlation coefficient test according to the type of parameter tested.

RESULTS

During the years 1996–2006 there were 131,218 live births at Soroka University Medical Center. Of these, 140 babies were born with orofacial cleft. This gives an overall incidence of 1.067/1000. During the study period 71,328 Bedouin babies were born of whom 110 had clefts, and of the 61,870 Jewish babies 30 were affected. The incidence of facial clefts was found to be 1.54/1000 and 0.48/1000 live births respectively ($P < 0.001$). Gender distribution of all cleft types was 54% male versus 46% female. However, there was a significant difference between females and males with regard to type of cleft ($P = 0.002$) [Table 1]. There was no difference in gender distribution and type of cleft between the two ethnic groups.

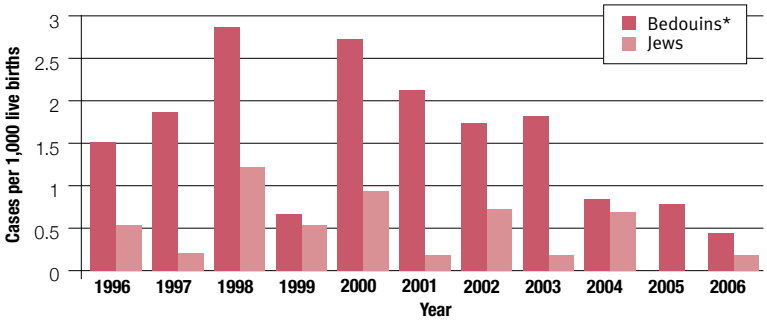
We found a significant decrease in the incidence of facial clefts for the 11 years under survey. When analyzing the decrease in incidence of cleft lip and cleft palate by ethnic group we observed that this decrease occurred more among the Bedouin (Spearman's Rho = -0.9) than in the Jewish population [Figure 1]. This is mainly attributed to a reduc-

Table 1. Distribution of facial cleft by type and gender

	Female		Male		Total	
	No. of cases	(%)	No. of cases	(%)	No.	(%)
Cleft palate	51	(36.4)	39	(27.9)	90	(64.3)
Cleft lip	9	(6.4)	20	(14.3)	29	(20.7)
Cleft lip & palate	4	(2.9)	17	(12.1)	21	(15)
Total	64	(45.7)	76	(54.3)	140	(100)

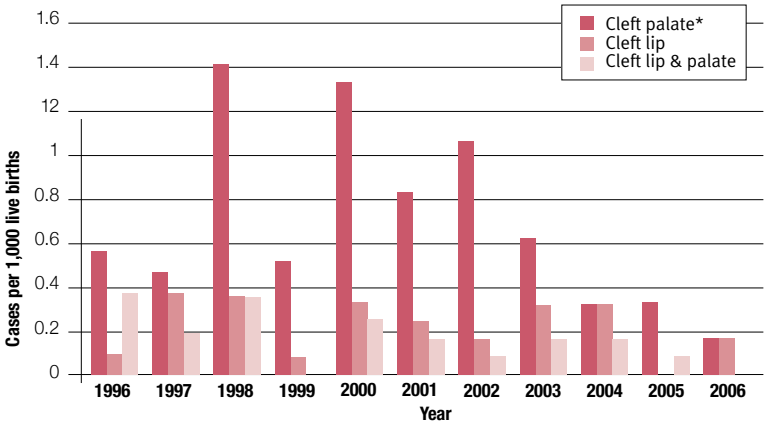
$P = 0.002$ (chi-square test)

Figure 1. Incidence of cleft lip and palate during 1996–2006



* Spearman's = -0.9 ($P < 0.01$)

Figure 2. Incidence of cleft lip and palate during 1996–2006



* Spearman's = -0.9 ($P < 0.01$)

Table 2. Incidence of facial clefts in the Middle East

Year	Country	Author [ref]	Incidence/1000 live births
1990	Kuwait	Srivastava and Bang [9]	1.48
1991	Saudi Arabia	Kumar et al. [10]	0.3
1992	Iran	Abbas and Taher [11]	3.73
2000	Iran	Rajabian and Sherkat [12]	1.03
2002	Israel	Jaber et al. [8]	1.56
2004	Jordan	Al-Omari and Al-Omari [13]	1.39
2005	Iran	Rajabian and Aghaei [14]	0.8

tion in the number of cleft palate cases, with an insignificant change in the number of cases of cleft lip or cleft lip and palate [Figure 2]. The change over years was true for male and female babies equally.

DISCUSSION

The present study is the first survey of babies with orofacial clefts born in the Negev region. The Negev region contains two major ethnic groups: Jews and Bedouins, who comprise about 84% and 16% of the Negev population, respectively. However, these two groups may be subdivided: the Bedouin into rather distinct tribes and the Jewish population by origin. With regard to natality, about 50% of newborns at Soroka are Bedouins. We found the overall incidence of facial clefts to be 1.067/1000 cases/live births, which is similar to other western and Middle Eastern communities [Table 2] [8-16]. When questioning the reliability of these data, we believe it accurately reflects the incidence in the Negev population, as we know from previous surveys that fewer than 6% of Negev mothers give birth in hospitals outside the region. Since according to National Social Insurance policy payment to the mother following a birth is given only when the baby is born in a hospital or is brought to hospital within 24 hours, a very negligible fraction of newborns are delivered outside a hospital and not brought to a hospital nursery.

In addition to the difference between Bedouins and Jews we notice a significant reduction in the incidence of orofacial clefts since 1998, with a peak of 2.08/1000 to 0.325/1000 live births in 2006. This trend is significant, is more pronounced in the Bedouin population, and occurs in cleft palate alone rather than cleft lip or cleft lip and palate. At present we do not have the data to explain this change over time, but it may be due to improvement in prenatal diagnosis or a decrease in consanguineous marriages in the Bedouin population. We do not believe that the latter has changed over such a short period, but we are witnessing a significant change in prenatal care in the Bedouin Negev population as part of social and health-related behavior changes.

Although isolated cleft lip and palate is not in itself an indication for abortion, prenatal diagnosis may reveal some associated syndromes and malformations that will motivate parents to terminate pregnancy. Prenatal ultrasound and the total care of clefts are entirely covered by the national health program; however, obviously in some cases the treatment will not be completed with a single surgical procedure and additional surgeries, orthodontics, speech therapy, etc., will be required. Our team routinely consults families where ultrasound has revealed an embryo with a facial cleft. We do not recommend terminating such a pregnancy as we have the records of hundreds of such children who were treated successfully and grew to become normal adults. Nevertheless, prenatal awareness regarding the expected cleft child will better prepare the family for the future ordeal of taking care of such a child and will leave the parents the option of terminating the pregnancy. Since many of these families are religious (Jews and Muslims) abortion is not an option, but being prepared will ease the initial trauma for the family and facilitate the acceptance and treatment of these children. The treatment of children with cleft lip and cleft palate continues to be a challenge to a multidisciplinary team of medical professionals. Understanding the epidemiology of our community may help in planning and providing better genetic consultation, prevention and care. The reduction in rates of congenital malformations, however, does not mean a reduction in the number of cases in a growing population. Also, with a modern western lifestyle, the expectations and demands for reconstructive facial surgery and comprehensive care for these children are on the rise.

Corresponding author:
Dr. E. Silberstein
Division of Plastic and Reconstructive Surgery, Soroka University Medical Center, P.O. Box 151, Beer Sheva 84101, Israel
Phone: (972-8) 640-0880
email: eldads@bgu.ac.il

References

1. Penfold CN. Cleft lip and palate evidence-based care. In: Booth PW, Schendel SA, Hausamen JE, eds. Maxillofacial Surgery. St. Louis, MO: Churchill Livingstone, 2007: 1000.
2. Zhu JL, Basso O, Hasle H, et al. Do parents of children with congenital malformations have a higher cancer risk? A nationwide study in Denmark. *Br J Cancer* 2002; 87: 524-8.
3. Christensen K, Juel K, Herskind AM, Murray JC. Long term follow up study of survival associated with cleft lip and palate at birth. *BMJ* 2004; 328: 1405.
4. Halevi HS. Congenital malformations in Israel. *Br J Prev Soc Med* 1967; 21: 66-77.
5. Azaz B, Koyoumdjisky-Kaye E. Incidence of clefts in Israel. *Cleft Palate J* 1967; 4: 227-33.
6. Tal Y, Dar H, Winter ST, Bar- Joseph G. Frequency of cleft lip and palate in northern Israel. *Isr J Med Sci* 1974; 10: 515-18.
7. Harlap S, Davies AM, Haber M, Rossman H, Prywes R, Samueloff N. Congenital

malformations in the Jerusalem perinatal study. *Isr J Med Sci* 1971; 7: 1520-8.

8. Jaber L, Nahmani A, Halpern GJ, Shohat M. Facial clefting in an Arab town in Israel. *Clin Genet* 2002; 61: 448-53.
9. Srivastava S, Bang RL. Facial clefting in Kuwait and England: a comparative study. *Br J Plast Surg* 1990; 43 (4): 457-62.
10. Kumar P, Hussain MT, Cardoso E, Hawary MB, Hassanain J. Facial clefts in Saudi Arabia: an epidemiologic analysis in 179 patients. *Plast Reconstr Surg* 1991; 88 (6): 955-8.
11. Abbas AY, Taher Y. Cleft lip and palate in Tehran. *Cleft Palate Craniofac J* 1992; 29 (1): 15-16.
12. Rajabian MH, Sherkat M. An epidemiologic study of oral clefts in Iran: analysis of 1,669 cases. *Cleft Palate Craniofac J* 2000; 37 (2): 191-6.
13. Al-Omari F, Al-Omari IK. Cleft lip and palate in Jordan: birth prevalence rate. *Cleft Palate Craniofac J* 2004; 41 (6): 609-12.
14. Rajabian MH, Aghaei S. Cleft lip and palate in southwestern Iran: an epidemiologic study of life births. *Ann Saudi Med* 2005; 25 (5): 385-8.
15. Borkar AS, Mathur AK, Mahaluxmivala S. Epidemiology of facial clefts in the central province of Saudi Arabia. *Br J Plast Surg* 1993; 46 (8): 673-5.
16. al-Bustan SA, el-Zawahri MM, al-Adsani AM, et al. Epidemiological and genetic study of 121 cases of oral clefts in Kuwait. *Orthod Craniofac Res* 2002; 5 (3): 154-60.

Capsule

Lowering LDL-cholesterol to levels below current recommendations may confer even more health benefits than statins alone

The use of statins to lower plasma levels of low density lipoprotein (LDL)-cholesterol can reduce the risk of cardiovascular disease by an estimated 30–40%. Yet some experts have argued that lowering LDL-cholesterol to levels below current recommendations – by co-administering drugs that act by a complementary mechanism, for example – may confer even more health benefits than statins alone. PCSK9 (proprotein convertase subtilisin/kexin type 9) is an appealing new drug target because it keeps plasma cholesterol levels high by promoting degradation of the receptor on liver cells that removes cholesterol from the blood. Interestingly, a small percentage of humans carry mutations in PCSK9 that reduce its activity and these individuals have a lower risk of heart disease, suggesting that therapeutic inhibition of PCSK9 will be safe. Stein et al. conducted small phase-1 trials of a human PCSK9 monoclonal antibody (REGN727) given to healthy volunteers and to individuals with familial and non-familial hypercholesterolemia. Injection of REGN727 induced no serious adverse effects in these short-duration trials, and in all groups the antibody significantly reduced LDL-cholesterol levels as compared with placebo.

N Engl J Med 2012; 366: 1108

Eitan Israeli

"Those who cannot forgive others break the bridge over which they themselves must pass"

Confucius (c. 551-478 BCE), Chinese philosopher and teacher

Capsule

The kinase Btk negatively regulates the production of reactive oxygen species and stimulation-induced apoptosis in human neutrophils

The function of the kinase Btk in neutrophil activation is largely unexplored. Honda et al. found that Btk-deficient neutrophils had more production of reactive oxygen species (ROS) after engagement of Toll-like receptors (TLRs) or receptors for tumor necrosis factor (TNF), which was associated with more apoptosis and was reversed by transduction of recombinant Btk. Btk-deficient neutrophils in the resting state showed hyperphosphorylation and activation of phosphatidylinositol-3-OH kinase (PI(3)K) and protein tyrosine kinases (PTKs) and were in a 'primed' state with plasma membrane-associated GTPase Rac2. In the absence of Btk, the adaptor Mal was associated with PI(3)K and PTKs at the plasma membrane, whereas in control resting neutrophils, Btk interacted with and confined Mal in the cytoplasm. These data identify Btk as a critical gatekeeper of neutrophil responses.

Nature Immunol 2012; 13: 369

Eitan Israeli

"Writing is easy. All you do is stare at a blank sheet of paper until drops of blood form on your forehead"

Gene Fowler (1890-1960), American journalist, author and dramatist