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Maternal-related factors in the origin of isolated cleft palate—A population-based case-control study

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Abstract

Objects: Isolated cleft palate (CPO) is the rarest form of oral clefting affecting 1-25 per 10 000 newborns worldwide. There is increasing evidence for the different pathogenetic backgrounds of CPO and cleft lip with or without cleft palate. The role of environmental factors in the origin of non-syndromic and syndromic CPO is unclear in most patients. The aim of this study was to estimate possible maternal risk factors in the origin of CPO.

Setting and Sample Population: The Hungarian Case-Control Surveillance of Congenital Abnormalities contains data of 32 345 birth defect cases and 57 231 control newborns. The study samples included 751 cases with isolated CPO, 1196 matched controls and 57 231 population controls.

Material and Methods: Maternal diseases during pregnancy in cases and population controls were compared, and adjusted ORs with 95% CI were calculated in a multivariable unconditional logistic regression model.

Results: Beyond the well-known robust female excess (58.9%)—maternal smoking (OR with 95% CI: 2.34, 1.94-2.81) medically recorded maternal anaemia, threatened abortion and excessive vomiting in pregnancy were associated with a higher risk for CPO in the offspring. An elevated risk was found in Graves' disease (OR: 4.30, 1.74-10.62), epilepsy (OR: 4.64, 2.44-8.82), migraine (OR: 2.82, 1.18-6.76) and essential hypertension (OR: 2.33, 1.32-4.10). Among acute diseases common cold (OR: 4.94, 3.48-7.03), acute respiratory infections (OR: 4.20, 1.49-11.82), influenza (OR: 2.95, 1.75-4.95), pulpitis (OR: 7.85, 2.80-22.03), cholecystitis (OR: 3.15, 1.16-8.60), acute urinary tract infections (OR: 4.08, 2.22-7.49) and pelvic inflammatory diseases (OR: 3.93, 1.62-9.53) during pregnancy also were associated with an increased risk for developing CPO.

Conclusion: The findings of this study suggest that maternal diseases and lifestyle factors during the first trimester play a significant role in the development of isolated cleft palate.

KEYWORDS

case-control study, cleft palate, maternal factors, pregnancy

1 | INTRODUCTION

Orofacial clefts are common birth defects, with an estimated worldwide incidence of around 1.7 per 1000 live born babies.[1] Hungarian data showed a cleft prevalence of 2.02/1000.[2] Babies born with these types of anomalies have feeding difficulties and are often developing conductive hearing loss, speech problems, dental anomalies and associated social and psychological issues.[3] Patients suffering from orofacial clefts may require multiple surgical, dental, orthodontic, speech, hearing and psychological treatments throughout childhood and adolescence.

Isolated cleft palate (cleft palate only, CPO) is the rarest form of oral clefting affecting 1-25 per 10 000 newborns worldwide.[4] There is increasing evidence for the different pathogenetic backgrounds of CPO and cleft lip with or without cleft palate (CL ± CP). CPO is frequently a component congenital abnormality (CA) in chromosomal aberrations or gene mutations (WNT3, TGIF, ZIC2, PTCH1, GLI2 and CDON).

Several candidate genes have also been identified in the origin of non-syndromic and syndromic CPO.[3,5]

However, the role of environmental factors is unclear in the vast majority of patients with CPO, except for the deleterious effect of smoking during pregnancy. Active or passive maternal smoking increases the risk of CPO with more than 25%.[6,7]

Thus, the aim of the present study was to estimate the role of maternal lifestyle factors (eg age, education and smoking) and acute or chronic maternal diseases during pregnancy in the origin of CPO, using the population-based Hungarian Case-Control Surveillance of Congenital Abnormalities (HCCSCA).

2 | MATERIALS AND METHODS

2.1 | The Hungarian Congenital Abnormality Registry (HCAR)

The HCAR was established in 1962 as the first national-based registry of CAs in the world.[8] Reporting of patients as cases with CA to the HCAR is mandatory for physicians from birth until the end of the first post-natal year. Most cases are reported by obstetricians and paediatricians (in Hungary, practically all deliveries occur at inpatient obstetric departments). Since 1984, pre-natal diagnostic centres were also asked to report malformed foetuses diagnosed pre-natally with or without elective termination of pregnancy to the HCAR. Two specialized geneticists of the HCAR examined the affected children. The physical examination contributed to CA-diagnosis confirmation and helped to differentiate the subgroups of CAs.

2.2 | The Hungarian Case-Control Surveillance of Congenital Abnormalities (HCCSCA)

Cases with CAs including CPO in the HCAR were enrolled to the HCCSCA if they met all the following selection criteria:

1. Reported to the HCAR within 3 months after birth or elective termination of pregnancy.
2. Did not have any of three mild CAs (dislocation of the hip, congenital inguinal hernia and large hemangioma).
3. Did not have CA-syndromes caused by gene mutations or chromosomal aberrations with pre-conceptional origin.

Controls were defined as newborn infants without CAs, and they were matched to cases according to sex, birth week and district of parents' residence. These controls were selected from the National Birth Registry of the Central Statistical Office based on case lists for each quarter of the years from the HCCSCA. In general, 2 controls were selected for each malformed newborn. If controls were twins, only one of them was randomly selected for the HCCSCA. In addition, if selected controls had any CA, these infants were excluded from the group of controls.

The HCCSCA was established in 1980. The collection of data was changed in 1997, slightly modifying the structure of the HCCSCA also. All data collected in the HCCSCA between 1980 and 2009 were unified into a validated single database that is now open for examination. This dataset of the HCCSCA is evaluated in this paper.

2.3 | Data collection

Data about maternal lifestyle factors, maternal diseases during pregnancy and occurrence of CPO were obtained via three sources:

1. *Prospective, medically recorded data.* Mothers were requested to send the pre-natal maternity logbook and every medical record concerning their diseases during the study pregnancy and their child's CA. Pre-natal care was mandatory for pregnant women; thus, nearly 100% of them attended pre-natal care, on average 7 times between the 6th gestational week and delivery. The task of obstetricians in pre-natal care was to record all maternal diseases and medicinal products used by women during the study pregnancy in the logbook.
2. *Retrospective, maternal self-reported information.* A structured questionnaire and a printed informed consent were also mailed to the mothers of cases and controls. It comprised questions regarding maternal diseases and related drug treatments, pregnancy supplements. Mothers were asked to read the enclosed list as a memory aid before they filled in the questionnaire and signed the informed consent.
3. *Supplementary data collection.* After 1996, regional nurses made home visits to all cases and controls. They helped mothers collect their medical records and fill in the questionnaire. The collection procedure was impugned by one mother in 2002 alluding to concerns of data privacy. The activity of the HCCSCA was stopped when the legal procedure started in 2003 and the HCCSCA could continue its work again only in 2005.

The following data are available for each case and control pregnancy: CA(s), gender, maternal age, paternal age, birth year/month/date, birthweight, gestational age, area of mother's living, birth order, mother's and father's qualification, employment status and type of employment, mother's marital status, outcome of previous pregnancies, maternal diseases during pregnancy (according to pregnancy months), drug intake during pregnancy (according to pregnancy months), mother's smoking habits and alcohol consumption patterns.

2.4 | Evaluation of cases with CPO

Cases with multiple/syndromic birth defects were excluded from the study.

Since the critical period of CPO is estimated to be between the 70th and the 99th post-conceptional days, that is 84th and 113rd gestational days calculated from the first day of the last menstrual period,[9] exposures were evaluated during the 3rd and 4th gestational months.[10] The effects of maternal illnesses were analysed if at least 0.5% of mothers were affected.

Controls were differentiated into two groups: matched controls (two controls were matched to the cases with CPO) and the so-called population controls including all controls in the HCCSCA.

2.5 | Statistical analysis

Quantitative variables such as mean maternal age and birth order were evaluated by Student's *t* test. Chi-squared test was used for the evaluation of maternal age distribution, birth order and employment status. For categorical variables, pregnancy complications, maternal diseases, drugs and pregnancy supplements adjusted odds ratios (OR) with 95% confidence intervals (CI) were estimated. A multivariable conditional logistic regression model was used to compare maternal risk factors of cases with matched controls. Maternal illnesses of cases and population controls were also compared and adjusted ORs with 95% CI were calculated in a multivariable unconditional logistic regression model. Among confounding factors maternal age (continuous variable), birth order (parity) (2 vs. 1, 3+ vs. 1) and employment status (skilled/semiskilled worker vs. professional/managerial, unskilled worker/other vs. professional/managerial) as an indicator of socioeconomic status were considered.[11]

3 | RESULTS

3.1 | General characteristics of the participants

In total, 2503 cases with orofacial clefts were identified in the HCCSCA between 1980 and 2009, among them 797 (31.8%) presenting with CPO at birth. Of these newborns, 46 cases (5.8%) with cleft palate diagnosed as part of multiple CA-syndromes were excluded from the analysis. Thus, 751 isolated CPO cases were evaluated. The number of matched controls was 1196. Live births in Hungary between 1980 and 2009 were 3 009 303; thus, 57 231 population controls represented 1.9% of all Hungarian births.

3.2 | Maternal lifestyle factors and CPO risk

Socio-demographic data of cases and controls are presented in Table 1. No significant differences between the case and control groups have been found in mean maternal or paternal ages, although the proportion of both younger and older mothers was lower in the CPO group as compared to matched controls.

The distribution of maternal employment status indicated a higher socioeconomic status of case mothers; however, these differences were also not significant. The proportion of managerial mothers was 19.9% (N = 149) in the group of cases and 14.5% (N = 173) in the group of matched controls, while that of unskilled mothers were 1.3% (N = 10) in the CPO group, 4.1% (N = 49) among matched controls and 3.5% (N = 2.022) in population controls. No significant differences were found in birth order (primiparous women: 371 [51.5%] vs. 595 [54.2%] and 28 301 (54.9%) in the control groups). The well-known gender differences among CPO cases were also verified in this database. Namely, CPO was significantly more common in females then males (442 [58.9%] females, 307 [40.9%] males, in 2 cases we found no data on gender). The birthweight of newborns affected by CPO was significantly lower than in the control groups (3076 vs. 3315 and 3295 g in matched and population controls, respectively).

A highly significant association has been found between maternal smoking and the development of CPO. The proportion of smoker mothers was 18.64% in the CPO group while 8.44% and 8.94% in the matched (OR: 2.5 [95% CI: 1.9-3.3]) and population (OR: 2.3 [95% CI: 1.9-2.8]) control groups, respectively.

3.3 | Maternal diseases during pregnancy and CPO risk

Among medically recorded pregnancy complications the incidences of anaemia (OR: 1.8 [95% CI: 1.3-2.7]), threatened abortion (OR: 4.9 [95% CI: 3.1-7.9]) and severe nausea-vomiting (OR: 3.2 [95% CI: 2.6-4.0]) were higher in the mothers of cases than in the mothers of matched controls. Detailed data are shown in Table 2.

The incidences of acute and chronic maternal disease groups with significantly altered odds ratios for CPO are presented in Table 3 and Table 4. Among acute illnesses various infectious, inflammatory diseases showed a higher incidence in the mothers of cases than in the mothers of matched and population controls (influenza (OR:1.8, 95% CI:1.3-2.5), acute upper respiratory infections (OR:2.5, 95% CI:1.9-3.1), acute lower respiratory infections (OR:2.4, 95% CI:1.4-4.2), urogenital infections (OR:2.0, 95% CI:1.4-2.8), etc, and unspecified high temperature (OR:8.1, 95% CI:2.9-22.6)). Besides this group, herpes simplex infection in the mothers also increased the risk of CPO significantly (OR:14.8, vCI:5.7-38.5).

TABLE 1 General characteristics of the cases, matched controls and population controls

	CPO (No: 751)		Matched controls (No: 1196)			Population controls (No: 57 231)		
	Mean	**SD**	**Mean**	**SD**	***P* values**	**Mean**	**SD**	***P* values**
Paternal age	29.35	6.33	29.49	6.29	.65	31.14	6.88*	<.01
Maternal age	26.62	4.46	26.34	5.83	.26	27.76	6.38*	<.01
	No.	**%**	**No.**	**%**		**No.**	**%**	
<23	184	24.53	375	31.35*	<.01	14 710	25.70	.06
23-33	482	64.27	611	51.09*	<.01	37 496	65.52	.06
>33	84	11.20	210	17.56*	<.01	5024	8.78	.06
Maternal education	**No.**	**%**	**No.**	**%**		**No.**	**%**	
Managerial	149	19.87	173	14.49	.32	11 057	19.32	.64
Professional	214	28.48	378	31.59	.32	17 166	29.99	.64
Skilled worker	209	27.81	322	26.96	.32	14 898	26.03	.64
Semiskilled	169	22.52	274	22.90	.32	12 088	21.12	.64
Unskilled	10	1.32	49	4.06	.32	2022	3.53	.64
Birth order	**No.**	**%**	**No.**	**%**		**No.**	**%**	
Primiparous	371	51.46	595	54.19	.25	28 301	54.90	.06
Multiparous	350	48.54	503	45.81	.25	23 249	45.10	.06
Gender	**No.**	**%**	**No.**	**%**		**No.**	**%**	
Male	307	40.93	492	41.13	<.01	37 006	64.66*	<.01
Female	442	58.93	704	58.86	<.01	20 179	35.26*	<.01
n.a.	2	0.27	1	0.08		46	0.08	
	Mean	**SD**	**Mean**	**SD**		**Mean**	**SD**	
Birthweight (g)	3076	451.65	3315*	387.00	<.01	3295*	398.34	<.01
Birth week	39.03	1.71	39.41*	1.35	<.01	39.7*	1.85	<.01
	No.	**%**	**No.**	**%**		**No.**	**%**	
Maternal smoking	140	18.64	101	8.44*	<.01	5114	8.94*	<.01

*$P < .05$.

The evaluation of chronic maternal diseases was based on medical records in the pre-natal maternity logbook again including at least 4 mothers of cases (0.5%). Maternal Graves' disease (OR:4.3, 95% CI:1.7-10.6), epilepsy (OR:4.6, 95% CI:2.4-8.8), migraine (OR:2.8, 95% CI:1.2-6.8), essential hypertension (OR:1.7, 95% CI:1.2-2.4) and neuro-musculoskeletal pain syndromes (OR:6.7, 95% CI:2.7-16.8) occurred more frequently in the mothers of 751 cases than in the mothers of matched or population controls. Similarly, elevated odds ratios for CPO have been found among mothers suffering from cholelithiasis (OR:5.6, 95% CI:2.2-13.8) or urolithiasis (OR:4.2, 95% CI:1.7-10.2).

TABLE 2 Number of pregnancy complications during the study pregnancy and the critical period of CPO in case mothers, matched and population control mothers and the risk of CPO

	Case mothers (N = 751)		Matched controls (N = 1196)		Comparison			Population controls (N = 57 231)		Comparison		
	No.	**%**	**No.**	**%**	**OR**	**95% CI***	***P* values**	**No.**	**%**	**OR**	**95% CI***	***P* values**
Anaemia complicating pregnancy	58	7.7	52	4.3	**1.84**	**1.25-2.71**	<.01	3942	6.9	1.13	0.86-1.48	.37
Threatened abortion	69	9.2	24	2.0	**4.94**	**3.08-7.94**	<.01	3331	5.8	**1.64**	**1.27-2.10**	<.01
Excessive vomiting in pregnancy	262	34.9	172	14.4	**3.19**	**2.56-3.98**	<.01	19 169	33.5	1.06	0.91-1.24	.42

Note: Significant differences in bold ($P < .05$).

TABLE 3 Number of acute maternal diseases during the study pregnancy and the critical period of CPO in case mothers, matched and population control mothers and the risk of CPO

	Case mothers (N = 751)		Matched controls (N = 1196)		Comparison			Population controls (N = 57 231)		Comparison		
	No.	%	No.	%	OR	95% CI*	*P* values	No.	%	OR	95% CI*	*P* values
Herpes simplex infection	5	0.7	0	0.0	n.a.			26	0.0	**14.75**	**5.65-38.51**	<.01
Common cold	124	16.5	46	3.8	**4.94**	**3.48-7.03**	<.01	4079	7.1	**2.58**	**2.12-3.13**	<.01
Acute upper respiratory infections	72	9.6	22	1.8	**5.66**	**3.48-9.21**	<.01	2372	4.1	**2.45**	**1.92-3.14**	<.01
Acute lower respiratory infections	13	1.7	5	0.4	**4.20**	**1.49-11.82**	<.01	414	0.7	**2.42**	**1.39-4.22**	<.01
Influenza	41	5.5	23	1.9	**2.95**	**1.75-4.95**	<.01	1762	3.1	**1.82**	**1.32-2.50**	<.01
Pulpitis	4	0.5	0	0.0	n.a.			39	0.1	**7.85**	**2.80-22.03**	<.01
Cholecystitis	4	0.5	0	0.0	n.a.			97	0.2	**3.15**	**1.16-8.60**	<.01
Acute urinary tract infections	37	4.9	15	1.3	**4.08**	**2.22-7.49**	<.01	1458	2.5	**1.98**	**1.42-2.77**	<.01
Pelvic inflammatory diseases	17	2.3	7	0.6	**3.93**	**1.62-9.53**	<.01	1051	1.8	1.24	0.76-2.01	.39
High temperature (unspecified)	4	0.5	1	0.1	6.40	0.71-57.36	.06	38	0.1	**8.06**	**2.87-22.64**	<.01

Note: Significant differences in bold ($P < .05$).

TABLE 4 Number of chronic maternal diseases during the study pregnancy and the critical period of CPO in case mothers, matched and population control mothers and the risk of CPO

	Case mothers (N = 751)		Matched controls (N = 1196)		Comparison			Population controls (N = 57 231)		Comparison		
	No.	%	No.	%	OR	95% CI*	*P* values	No.	%	OR	95% CI*	*P* values
Thyrotoxicosis (Graves' disease)	5	0.7	0	0.0	n.a.			89	0.2	**4.30**	**1.74-10.62**	<.01
Epilepsy	10	1.3	0	0.0	n.a.			166	0.3	**4.64**	**2.44-8.82**	<.01
Migraine	14	1.9	8	0.7	**2.82**	**1.18-6.76**	<.01	694	1.2	1.55	0.91-2.64	.10
Essential (primary) hypertension	30	4.0	21	1.8	**2.33**	**1.32-4.10**	<.01	1375	2.4	**1.69**	**1.17-2.44**	<.01
Constipation	11	1.5	3	0.3	**5.91**	**1.64-21.26**	<.01	571	1.0	1.48	0.81-2.69	.20
Cholelithiasis	5	0.7	0	0.0	n.a.			97	69	**5.55**	**2.23-13.80**	<.01
Neuro-musculoskeletal pain syndromes	5	0.7	0	0.0	n.a.			54	57	**6.72**	**2.69-16.82**	<.01
Urolithiasis	5	0.7	2	0.2	4.00	0.77-20.68	.07	92	0.2	**4.16**	**1.69-10.27**	<.01

Note: Significant differences in bold ($P < .05$).

4 | DISCUSSION

The aim of the present study was to investigate the association of maternal diseases and lifestyle factors with the risk of CPO based on the comparison of mothers of cases and matched and population controls.

Analysing the socio-demographic data a role of higher paternal age in the development of CPO could not be identified, although a causative role had previously been described.[12,13] Active or passive maternal smoking is a well-known risk factor in CPO occurrence[6,7] Our results are in accordance with the previous findings; however, in this study, odds ratios of maternal smoking were 2.5 and 2.3 as compared to the matched and population control groups, respectively. On the other hand, Lorente et al could not show the elevated risk of CPO among tobacco using mothers.[14]

The possible correlation between cleft palate and lower birthweight needs to be clarified in further studies; however, the

significantly higher rate of maternal smoking among CPO mothers may play a role in growth restriction. The present findings revealed a significantly lower birthweight of infants with CPO as compared to the control groups. The same trend has been described in populations in Iran,[15] Taiwan[16] and Uganda.[17]

In the present study, a significant difference was shown in the development of CPO between anaemic and non-anaemic mothers. Literature data on this correlation are scarce. Similarly, but non-conclusive findings were published in India and in Japan.[18,19] The deleterious effect of anaemia may be a consequence of embryonic hypoxia during the first trimester, since it has been described that hypoxia may result in insufficient growth of the facial processes in the developing embryo.[20] The possible role of threatened abortion in the development of cleft palate was already described more than 40 years ago[21] but since then similar findings have not been presented. In the study, dataset threatened abortion significantly increased the risk of developing CPO as compared either to matched or population controls. The theoretical pathomechanical background may be insufficient levels of progesterone or human chorionic gonadotrophin (hCG).

An interesting elevation in the risk of CPO among mothers suffering from excessive vomiting in the first 4 months of pregnancy was observed. The risk was significantly higher in cases than matched controls. However, this difference did not occur by comparing the case group to population controls. Excessive vomiting was accepted during the analysis if hyperemesis was recorded by the obstetrician in the pregnancy logbook. Hyperemesis in pregnancy is generally believed to exert a protective effect against miscarriages, preterm birth.[22] Nausea and vomiting during pregnancy were also supposed to play a protective role against the development of some birth defects, for example cleft lip.[23] The most widely accepted hypothesis explains the beneficial effects of nausea and vomiting by a larger placenta and a higher blood level of human chorionic gonadotropin and estrogens in hyperemetic pregnant women. This hormonal milieu may have a protective effect against some CAs. On the other hand, in accordance with our results, an association between severe nausea and vomiting in early pregnancy and the risk of neural tube defects have been described in Northern China.[24]

Acute maternal diseases that caused an elevated risk for CPO show a typical pattern, namely all of them are infectious diseases of various organs. The common causative pathway may be the presence of hyperthermia since high fever-related maternal diseases are supposed to result in an increased prevalence of birth defects.[25] However, the possible role of inflammatory cytokines must also be taken into consideration (eg pulpitis is generally not associated with high temperature, but it also caused an elevated risk for CPO). The role of influenza during pregnancy in the development of CPO should be emphasized, since this infection may be effectively prevented by vaccination.

Among chronic maternal diseases present during the first 14 weeks of pregnancy, a higher risk of CPO was found among mothers suffering from hyperthyroidism as compared to population controls. We are not aware of similar observations in the literature, although the importance of better reporting congenital anomalies in children of mothers with Graves' disease has already been emphasized.[26] In women with epilepsy, it is known that the risk of birth defects in general and orofacial clefts in their offspring is significantly elevated. Present results are in accordance with the literature data.[27,28] It is important to note that the possible teratogenic effect of antiepileptic drugs in these cases must also be taken into consideration.[29,30] An elevated risk of CPO in mothers with migraine was also presented. Some earlier studies could not identify any deleterious effect of maternal migraine on the development of birth defects,[31] but the analysis of the first part of the HCCSCA has already shown this increased risk.[32] In the case of maternal migraine, it is not clear whether the elevated risk of cleft formation is a consequence of the illness itself or of the drugs used to alleviate its symptoms.[33] Our present findings showed an increased risk of CPO among mothers suffering from cholelithiasis, urolithiasis or neuro-musculoskeletal pain syndromes as well. There are no available literature data reassuring this finding; thus, it may be supposed that this effect is caused by the use of pain killers or spasmolytic drugs.

The strengths of our study are connected with the large population-based dataset of the HCCSCA in an ethnically homogeneous Hungarian (Caucasian) population. The CPO diagnosis has high accuracy (or reliability) since cases were reported by medical doctors in the HCAR and the diagnosis was accepted in all cases within the dataset of the HCCSCA. This study included all acute and chronic maternal diseases and these exposure data were based on multiple sources including pre-natal maternity logbooks, which provided prospective medically recorded data. The exposure time and potential confounders were known.

However, there are also some limitations of our study. Maternal diseases, lifestyle factors and pregnancy supplementations were based partly on retrospective maternal information burdened by recall bias.[34] However, we accepted these associations only if they were confirmed by prospective medically recorded data. Another weakness of our study is that only cases born between 1980 and 2009 were evaluated; thus, the results of recent medical progress could not be analysed in this field.

5 | CONCLUSIONS

Maternal smoking, anaemia, hyperemesis, acute inflammatory diseases, influenza, Graves' disease, epilepsy, migraine, essential hypertension, neuro-musculoskeletal pain syndromes, cholelithiasis and urolithiasis occurred more frequently in the mothers of cases than in the mothers of matched or population controls. In conclusion, the findings of this study suggest that maternal lifestyle factors and diseases during the first trimester play a significant role in the development of isolated cleft palate.

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CONFLICT OF INTEREST

The authors declare no conflict of interest.

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