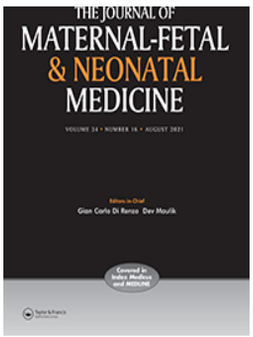

The Journal of Maternal-Fetal & Neonatal Medicine

ISSN: 1476-7058 (Print) 1476-4954 (Online) Journal homepage: https://www.tandfonline.com/loi/ijmf20

First data from the new, unified database of the Hungarian case-control surveillance of congenital abnormalities

Nándor Ács, Ákos Mátrai & András Kaposi

To cite this article: Nándor Ács, Ákos Mátrai & András Kaposi (2019): First data from the new, unified database of the Hungarian case-control surveillance of congenital abnormalities, The Journal of Maternal-Fetal & Neonatal Medicine, DOI: 10.1080/14767058.2019.1673359

To link to this article: https://doi.org/10.1080/14767058.2019.1673359

Published online: 15 Oct 2019.

THE JOURNAL OF MATERNAL-FETAL & NEONATAL MEDICINE
https://doi.org/10.1080/14767058.2019.1673359

Taylor & Francis
Taylor & Francis Group

ORIGINAL ARTICLE

First data from the new, unified database of the Hungarian case-control surveillance of congenital abnormalities

Nándor Ács[a], Ákos Mátrai[a] and András Kaposi[b]

[a]Department of Obstetrics and Gynaecology, Semmelweis University School of Medicine, Budapest, Hungary; [b]Department of Biophysics and Radiation Biology, Semmelweis University School of Medicine, Budapest, Hungary

ABSTRACT

The Hungarian Case-Control Surveillance of Congenital Abnormalities (HCCSCA) is one of the largest case-control data sets of CA-surveillance in the world. We unified all data collected in the HCCSCA between 1980 and 2009 into a new, validated single database that is now open for examination. The details of this unified database are given in this paper. The total number of cases and control newborns is 32,345 and 57,231, respectively. The overall prevalence of CAs recorded in the HCCSCA was 10.7/1000 live-births. Data available for each pregnancy are: CA(s), gender, birth year/month/date, birth weight, gestational age, area of mother's living, maternal age, paternal age, 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), folic acid and/or pregnancy vitamin supplement intake (according to pregnancy months), mother's smoking habits and alcohol consumption patterns. The most frequent anomalies detected were ventricular septal defect (2864), atrial septal defect (1895), polydactyly (1499), hypospadias (1083), and unilateral cleft lip ± palate (961). According to ICD-10, 701 diseases have been found to affect case mothers during pregnancy. Eight hundred and sixteen drugs were identified that had been taken by mothers during pregnancy. The authors are absolutely open for any scientific cooperation based on this database.

ARTICLE HISTORY
Received 7 August 2018
Revised 31 October 2018
Accepted 24 September 2019

KEYWORDS
Birth defect; case control; database; drug intake; maternal disease

Introduction

Mandatory notification of newborns with different congenital abnormalities (CAs) in Hungary was ordered by the Ministry of Health in 1962. This disposition was warranted by the greatest tragedy of human teratology, the thalidomide (Contergan) disaster. A traditional mandatory notification system for infectious diseases had been working in Hungary for years, but the significance of CAs in infant mortality was found to be fourfold higher than that of infectious diseases. Thus, Hungary established the first national-based registry of CAs in the world.

However, it soon became clear that the evaluation of these cases needed epidemiological expertise. Therefore, based on international recommendations [1] this registry was further developed and formed the base of the Hungarian Congenital Abnormality Registry (HCAR) at the National Institute of Public Health (NIPH) from 1970 [2]. After having detected certain CA clusters by the HCAR, population-based surveillance of cases with CA and controls, the Hungarian Case-Control Surveillance of Congenital Abnormalities (HCCSCA) was established in 1980 [3]. This registry worked in its original form until 1996. The professional network led by Czeizel thoroughly analyzed the data of these 17 years, publishing more than 800 scientific papers based on this database.

The collection of data was changed in 1997, slightly modifying the structure of the HCCSCA also. Cases and controls notified after 1997 formed another voluminous database that has not been analyzed yet. Therefore, first, we examined and validated the records of this second part of the HCCSCA. After that, we solved the problem of differences between the structures of the two chapters. Finally, we managed to unify all data collected in the HCCSCA between 1980 and 2009 into a validated single database that is now

CONTACT Nándor Ács acsnandor@gmail.com Department of Obstetrics and Gynecology, Semmelweis University School of Medicine, Ulloi ut 78/a, Budapest, Hungary

open for examination. The details of this unified database are given in this paper.

Materials and methods

Study groups

Cases with CA were selected from the HCAR. Three exclusion criteria were used at the selection for the data set of the HCCSCA:

- Cases reported after 3 months of birth or pregnancy termination. This subgroup included 33% of cases affected mainly by mild CAs. This shorter time between birth or pregnancy termination and data collection increases the accuracy of maternal information regarding the data of study pregnancy without undue loss of power.
- Three mild CAs (such as congenital dysplasia of hip, congenital inguinal hernia, and large hemangioma), because their prevalence is high with low completeness of notification. Moreover, these CAs had been studied in descriptive and case-control epidemiological studies previously.
- CA-syndromes caused by major mutant genes or chromosomal aberrations. The origin of these CA-syndromes is preconceptional and the main task of the HCCSCA has been the detection of teratogenic/fetotoxic agents during pregnancy.

Matched controls without CAs were chosen from the National Birth Registry of the Hungarian Central Statistical Office until 1996. After 1997, specially trained regional nurses selected controls from the area of cases according to strictly determined principles. Controls were defined as newborns without any CA. In most years, two controls were matched to every case according to sex, birth week in the year when the case was born, and district of parents' residence. Three controls were selected for each case between 1986 and 1992. However, after 1992, the third control was left due to insufficient financial support.

The group of malformed controls included cases with Down's syndrome selected from the HCAR. Malformed controls were also chosen during the first 3 months after birth or pregnancy termination. Ninety-four percent of these cases had pure trisomy 21 caused by nondisjunction before conception. The explanation for the use of this malformation control group is that their mothers have better recall for the events during pregnancy similar to the mothers of cases. The origin of Down's syndrome is preconceptional, thus, teratogenic/fetotoxic agents cannot modify its manifestation.

Collection of exposure and other data

The three following data sources were used.

Prospective medically recorded data

An explanatory letter with an informed consent form was mailed to the mothers immediately after the selection of cases, controls, and malformed controls to explain the importance of this project. Mothers were asked to send us the prenatal care logbook and other medical records (mainly discharge summaries of their hospitalizations) concerning their diseases and related drug treatments during the study pregnancy and their child's CA. These documents were sent back within a month. In Hungary, nearly 100% of pregnant women visit prenatal care with the first visit at 6–12 weeks of gestation and with an average of seven visits. During prenatal care visits, obstetricians record all pregnancy complications, maternal diseases, and prescribed drugs in the prenatal care logbook.

Retrospective self-reported maternal information

A printed structured questionnaire with a list of medicines and diseases was also sent to the mothers of cases, controls, and malformed controls. The questionnaire requested information on their marital end employment status, drug, and pregnancy supplement intakes, pregnancy complications and maternal diseases during pregnancy. Family history of CAs and history of their previous pregnancies were also recorded. To standardize the answers, mothers were asked to read the enclosed list of drugs and diseases as memory aid before they replied.

Supplementary data collection

After 1996, all cases and controls were visited at home by regional nurses. These regional nurses helped mothers to collect their medical records and fill in the questionnaire. This collection procedure was impugned by one mother in 2002 alluding 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.

Types of data recorded

The following data are available for each case and control pregnancy: CA(s), gender, birth year/month/date, birth weight, gestational age, area of mother's

living, maternal age, paternal age, 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), folic acid and/or pregnancy vitamin supplement intake (according to pregnancy months), mother's smoking habits and alcohol consumption patterns.

Unifying the two segments of the database

According to computing standards of those decades, data were collected into text files between 1980 and 1996. From 1997, these data were recorded using Microsoft Excel datasheets. Slight coding differences were also present between the two segments of the database. Therefore, as the first step, data of the first 17 years were converted from text files into Excel sheets. Coding differences were also resolved, and data were validated excluding erroneously recorded cases and controls. Finally, the two segments of the database were united into one single datasheet.

Statistical analysis

The software R was used for the analysis of variables (Vienna, Austria). At the evaluation of quantitative variables such as mean maternal age and birth order, Student's *t*-test was used. We used chi-square test at the evaluation of distribution of maternal age, birth order, and employment status. At the evaluation of categorical variables: pregnancy complications, maternal diseases, drugs and pregnancy supplements adjusted odds ratios (ORs) with 95% confidence intervals (CIs) were estimated. At the comparison of mothers of cases and matched controls, a multivariable conditional logistic regression model was used. The exposures in the mothers of cases and population controls were also compared and adjusted ORs with 95% CI were calculated in the multivariable unconditional logistic regression model. Among confounding factors, maternal age (continuous variable), birth order (parity) (2 versus 1, 3+ versus 1) and employment status (skilled/semiskilled worker versus professional/managerial, unskilled worker/other versus professional/managerial) as indicator of socioeconomic status were considered [4].

Results

The mean time elapsed between the end of pregnancy and return of the "information package" (including prenatal logbook, questionnaire, signed informed consent, etc.) was 3.5 ± 1.2, 5.2 ± 2.9, and 3.3 ± 1.8 months in the case, control, and malformed control groups, respectively.

Table 1. Numbers of case and control mothers in the Hungarian Case-Control Surveillance of Congenital Abnormalities (HCCSCA).

Study groups	1980–1996	1997–2008	Total
Cases	22,730	9615	32,345
Controls	36,944	20,287	57,231
Total	59,674	29,902	89,576

The numbers of cases and controls collected in the HCCSCA are presented in Table 1. Altogether, we have 32,345 cases and 57,231 controls recorded in our database. During the study period, there were 3,009,303 live-births in Hungary, thus our control sample represented 1.9% of total births. The overall prevalence of CAs recorded in the HCCSCA during the study period was 10.7/1000 live-births (as mentioned earlier, some mild CAs of high prevalence, but of limited clinical relevance were excluded from the database). The age of mothers was 26.1 ± 5.5 years and 27.5 ± 8.4 years in the case and control groups, respectively.

The detailed numbers of specific CAs and CA groups in the HCCSCA are given in Table 2. The most frequent anomalies detected were ventricular septal defect (2864), atrial septal defect (1895), polydactyly (1499), hypospadias (1083), and unilateral cleft lip ± palate (961).

According to ICD-10, altogether we found 701 diseases that affected case mothers during pregnancy. The most frequently detected diseases among case and control mothers are given in Table 3. The top five among case mothers were: common cold: 4498, acute upper respiratory infections: 3026, acute urinary tract infections: 2265, influenza: 1540, and hypertension: 1365.

We identified 816 drugs that were taken by mothers during pregnancy. Apart from vitamin intake, the most prevalent ones are shown in Table 4. The five most frequently taken drugs were: iron supplements: 19,028, magnesium supplements: 4418, promethazine: 4018, allylestrenol: 3743, and diazepam: 2985.

Discussion

According to our knowledge, until now, the HCCSCA has become one of the largest case-control data sets of CA-surveillance in the world. This is an open source of data for any researcher in the field.

The merit of the HCCSCA is not only limited to its size but it has a remarkable quality of data as well.

Table 2. Numbers of specific CAs and CA groups in the HCCSCA.

Cardiovascular CAs	8775
Ventricular septal defect	2864
Atrial septal defect	1895
Unspecified CA of the heart	781
Patent ductus arteriosus	701
Other specified atrio-ventricular CAs	337
Tetralogy of Fallot	290
Stenosis of pulmonary artery	228
Coarctation of aorta	209
Other CAs of aorta	176
Pulmonary artery atresia	133
Transposition of great vessels	125
Hypoplastic left heart syndrome	124
Atrio-ventricular septal defect	118
CAs of the musculoskeletal system	7589
Polydactyly	1499
Syndactyly	1042
Clubfoot	601
Congenital limb deficiencies	635
Torticollis	375
CAs of the diaphragm	270
CAs of the genital organs	5030
Hypospadias	1083
Undescended testis	762
Cleft lip ± palate	2505
Cleft lip ± palate (unilateral)	961
Cleft palate	754
Cleft lip (unilateral)	682
Cleft lip ± palate (bilateral)	38
Posterior cleft palate	19
Cleft lip (bilateral)	11
Neural tube defects	2024
Spina bifida without hydrocephaly	678
Encephalocele	508
Anencephaly	314
Spina bifida with hydrocephaly	150
Microcephaly	145
Congenital hydrocephaly	82
Corpus callosum agenesis	22
Gastrointestinal CAs	1501
Cong. hypertrophic pyloric stenosis	275
Atresia/stenosis of colon	219
Esophageal atresia/stenosis	209
Atresia/stenosis of small intestine	195
CAs of the urinary tract	1381
Obstructive CAs of the pelvis/ureter	382
Cystic kidney disease	200
Renal agenesis/dysgenesis	228
Congenital hydronephrosis	109
CAs of the ear	536
Congenital deafness	305
Accessory auricle	61
Absence of auricle	37
Absence/atresia of auditory canal	27
CAs of the eye	171
Congenital cataract	53
Microphthalmos	30
Congenital disorders of the cornea	21
Congenital glaucoma	19
Congenital coloboma	13
Anophthalmia	8
Head and neck CAs	95
CAs of the skin	92
Broncho-pulmonary CAs	92
Pulmonary hypoplasia/dysplasia	47
Naso-pharyngeal CAs	66
Multiple CAs	1935

The surveillance is population-based (the population of Hungary is about 10 million), and the validity of CAs is excellent due to hospitalization for delivery. In Hungary, more than 99% of deliveries take place at obstetrical inpatient departments; therefore, birth weight and gestational age are always medically recorded. Nearly, all infant deaths are autopsied; thus, congenital anomalies are validated by pathologists. In addition, the diagnoses of CAs were reported by

Table 3. Maternal diseases during pregnancy affecting at least 100 case mothers in the Hungarian Case-Control Surveillance of Congenital Abnormalities (HCCSCA).

	Cases	Controls
Common cold	4498	5910
Anemia during pregnancy	4066	8064
Acute upper respiratory infections	2902	4009
Acute urinary tract infections	2265	3196
Influenza	1540	2049
Hypertension	1022	1541
Candidal stomatitis (oral thrush)	825	1650
Hemorrhoids	805	1557
Varicose veins of lower extremities	770	1567
Migraine	585	720
Hypertensive heart disease	573	1070
Pelvic inflammatory disease	550	873
Headache	539	1250
Acute vaginitis	526	825
Hypotension	523	1170
Obstipation	454	784
Gestational diabetes	301	459
Allergic rhinitis	276	530
Anxiety disorder	211	179
Cardiac arrhythmia	144	181
Unspecified viral infection	139	104
Epilepsy	136	125
Urogenital trichomoniasis	134	134
Bronchial asthma	128	208
Pneumonia	124	179
Acute cholecystitis	105	141
Allergic rash	100	173

Table 4. Drug intake of mothers during pregnancy (25 most frequent ones) in the Hungarian Case-Control Surveillance of Congenital Abnormalities (HCCSCA).

	Cases	Controls
Iron supplements	19,028	35,094
Magnesium supplements	4418	8478
Promethazine	4018	6527
Allylestrenol	3743	5701
Diazepam	2985	4412
Terbutaline	2567	4281
Drotaverine	2336	3886
Micronized progesterone	2322	4739
Ampicillin	2045	3163
Clotrimazole	1929	3482
Penamecillin	1734	2337
Metamizole	1703	2135
Diaphyllin	1563	2537
Ergocalciferol	1556	3095
Metronidazole	1315	1988
Sulfamethoxazole + trimethoprim	1133	897
Acetylsalicylic acid	1004	1369
Diphenhydramine	973	1777
Nitrofurantoin	808	1122
Oxedrine	777	1479
Oxerutine	758	1416
Bromhexine	515	829
Methyldopa	514	814
Clopamide	498	916
Aminophenazone	491	718

medical doctors and underwent several checking procedures by experts. Each CA case has at least two matched controls without any CA. In general, the diagnoses of maternal diseases are also scientifically accurate due to mandatory prenatal care in Hungary. Most maternal diseases were recorded prospectively by medical doctors in the prenatal logbook.

The overall prevalence of CAs recorded in the HCCSCA (10.7/1000 live-births) may seem to be surprisingly low. In the last decade, the average yearly prevalence of CAs in the HCAR was 26.4/1000, that is in congruence with international data [5]. This obvious difference may be the consequence of (a) the exclusion criteria mentioned in Materials and methods (late reporting, excluded common, mild CAs, and chromosomal aberrations) and (b) missed reporting of cases.

The first part of this database (1980–1996) has been thoroughly analyzed resulting in more than 800 peer-reviewed papers. However, the collection of data was changed in 1997, slightly modifying the structure of the HCCSCA also. Cases and controls notified after 1997 formed another voluminous database that has not been analyzed yet. After having solved the problem of differences between the structures of the two chapters, we unified all data collected in the HCCSCA into a validated single database that is now open for examination.

It is obvious that the prenatal diagnosis of birth defects had been significantly improved during the recording of the two chapters of our database as a result of new imaging technologies [6–9]. We could also observe a dramatic change in genetic testing in the last two decades. The use of traditional karyotyping, noninvasive prenatal tests (NIPTs) and chromosomal microarray analysis (CMA) became widespread and available in the developed world [10–12]. Improved detection using the new imaging techniques and the increasing number of detected chromosomal anomalies obviously result in better detection rates of fetal abnormalities. Therefore, the prevalence of terminations of pregnancy following prenatal diagnosis (TOPFA) is increasing.

One of the shortcomings of the Hungarian database is that although it contains precise and detailed data on pregnancy, at the moment we are not able to systematically integrate data on postnatal follow-up (either clinical or chromosomal testing) of these malformed newborns. However, if a chromosomal abnormality is verified, that case is not included in our database, since the origin of these CA-syndromes is preconceptional and the main task of the HCCSCA has been the detection of teratogenic/fetotoxic agents during pregnancy.

The complete database now includes an additional 9615 deliveries with CAs and 20,287 control newborns; altogether, 29,902 new pregnancies were recorded after the analyses of the first part of the HCCSCA. Thus, we are able to expand the previous results with much larger sample sizes to include the more recent data. The addition of these data also allows for greater power to detect associations between various maternal illnesses, drug intakes, and other factors and less frequent birth defects. The immense amount and the excellent validity of data included in our database probably make the HCCSCA a unique source of scientific information. The detailed analyses of our data will be presented in further papers in the near future. The purpose of this manuscript is to show the research opportunities provided by this newly available database. We are absolutely open for any scientific cooperation based on these data.

Acknowledgments

The authors would like to express their deep honor to late Dr. Andrew E. Czeizel, the founder of the HCCSCA. Andrew was a great scientist and a true gentleman, his friendship was one of the greatest gifts of our life. Without his enormous work, these studies could not have been performed.

Disclosure statement

No potential conflict of interest was reported by the authors.

Funding

This study was partly sponsored by a grant from the Hungarian Scientific Research Fund [OTKA 112829].

ORCID

Nándor Ács http://orcid.org/0000-0002-1919-1869

References

[1] Miller JR. Some uses of genetic registries. In: Emery AEK, Miller JR, editors. Registers for the detection and prevention of genetic diseases. New York: Stratton Int. Med. Book Co; 1976.

[2] Czeizel AE. First 25 years of the Hungarian Congenital Abnormality Registry. Teratology. 1997; 55(5):299–305.

[3] Czeizel AE, Rockenbauer M, Siffel C, et al. Description and mission evaluation of the Hungarian Case-Control Surveillance of Congenital Abnormalities, 1980–1996. Teratology. 2001;63(5):176–185.

[4] Puhó E, Métneki J, Czeizel AE. Maternal employment status and isolated orofacial clefts in Hungary. Cent Eur J Public Health. 2005;13(3):144–148.
[5] Dolk H, Loane M, Garne E. The prevalence of congenital anomalies in Europe. Adv Exp Med Biol. 2010;686: 349–364.
[6] Yeo L, Romero R. Color and power Doppler combined with Fetal Intelligent Navigation Echocardiography (FINE) to evaluate the fetal heart. Ultrasound Obstet Gynecol. 2017;50(4):476–491.
[7] Barišić LS, Stanojević M, Kurjak A, et al. Diagnosis of fetal syndromes by three- and four-dimensional ultrasound: is there any improvement? J Perinat Med. 2017;45(6):651–665.
[8] Matos APP, Duarte LB, Castro PT, et al. Evaluation of the fetal abdomen by magnetic resonance imaging. Part 1: malformations of the abdominal cavity. Radiol Bras. 2018;51(2):112–118.
[9] Castro P, Paula Matos A, Werner H, et al. Prenatal diagnosis of suprarenal mass by magnetic resonance imaging: a case series. J Matern Fetal Neonatal Med. 2019;32(22):3882–3886.
[10] Wapner RJ, Martin CL, Levy B, et al. Chromosomal microarray versus karyotyping for prenatal diagnosis. N Engl J Med. 2012;367(23): 2175–2184.
[11] Allen S, Young E, Bowns B. Noninvasive prenatal diagnosis for single gene disorders. Curr Opin Obstet Gynecol. 2017;29(2):73–79.
[12] Levy B, Wapner R. Prenatal diagnosis by chromosomal microarray analysis. Fertil Steril. 2018; 109(2):201–212.