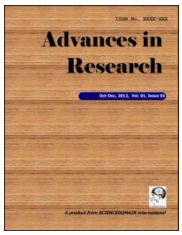

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Birth Outcomes of Cases with Single Ventricle Complex – A Population-Based Case-Control Study

Attila Vereczkey[1], Melinda Csáky-Szunyogh[2], Balázs Gerencsér[3] and Andrew E. Czeizel[4*]

[1]Versys Clinics, Human Reproduction Institute, Budapest, 1138, Madarász Viktor utca 47-49, Hungary.
[2]National Centre for Healthcare Audit and Inspection, Budapest, 1096, Nagyvárad tér 2. Hungary.
[3]Alfréd Rényi Institute of Mathematics, Hungarian Academy of Science, Budapest, 1053, Reáltanoda utca 13-15, Hungary.
[4]Foundation for the Community Control of Hereditary Diseases, Budapest 1026, Törökvész lejtő 32, Hungary.

Authors' contributions

This work was carried out in collaboration between all authors. Author AEC established the Hungarian Case-Control Surveillance of Congenital Abnormalities (HCCSCA), was the director of the HCCSCA between 1980 and 1996, and provided the data of the HCCSCA for analysis of authors AV and MCS visited cardiologic institutions and revised the data of patients with congenital heart defects. Author BG did the mathematical analysis. Authors AV and AEC wrote the paper. All authors read and approved the final manuscript.

Original Research Article

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ABSTRACT

Aims: The aim of this paper was to study the birth outcomes of cases with single ventricle complex (SVC), a rare congenital heart defect, as homogeneously as possible.
Study Design: For the analysis of cases, the large dataset of the population-based Hungarian Case-Control Surveillance of Congenital Abnormalities was used.
Place and Duration of Study: The study was conducted in Budapest based on the data set of the HCCSCA between 1980 and 1996 but the follow-up of cases was performed in

**Corresponding author: E-mail: czeizel@interware.hu;*

2008-2011.
Methodology: Syndromic/multiple cases with the component SCV were excluded and only live-born cases based on autopsy report in lethal cases and on medical documents after surgical correction were included to the study. Medically recorded birth outcomes of 76 cases with SVC and 38,151 population controls without defect were compared but maternal socio-demographic variables as confounders were considered.
Results: A higher rate of twins (5.3% vs. 1.0%; OR with 95% CI: 5.11, 1.55-12.40) was observed in cases compared to population controls. The rate of low birthweight (18.4% vs. 5.7%; OR with 95% CI: 4.84, 2.23-9.71) was higher in cases than in population controls. Among maternal variables the higher birth order 3 or more (25.0% vs. 14.8%, p=0.04) and pregnancy order (p = 0.0005) are noteworthy, the latter is explained by the higher rate of miscarriages in previous pregnancies of case mothers.
Conclusion: The higher rate of twins and low birthweight suggest some association with the origin of SCV.

Keywords: Single ventricle complex; twins; low birthweight; birth/pregnancy order; population-based case-control study.

1. INTRODUCTION

Congenital heart defects (CHD) are the most prevalent and some of the most serious structural congenital abnormalities (CAs), with profound medical, psychosocial and economic consequences. Among 1000 live-births, 4-50 were affected with CHD in different studies [1,2], and in Hungary this rate was 10.2±2.1 per 1000 births [3]. Though there was a significant progress in the care of infants/children with CHD, CHD are a major factor in children mortality [4,5]. The revolution of genetics helped us to better understand the genetic background of CHD [6], but the role of possible environmental factors is unclear in the vast majority of patients [7].

At the evaluation of CHD, the first task is to differentiate groups and entities of CHD according to etiology [8]. As a second step, the so-called isolated (only heart and great vessels affected) and multiple-syndromic (CHD associated with other non-cardiac CA) cases should be separated. The aim of this study was to evaluate the birth outcomes of cases with a rare type of isolated CHD, i.e., single ventricle complex (SVC), in the population-based Hungarian Case-Control Surveillance of Congenital Abnormalities (HCCSCA) [9].

2. MATERIALS AND METHODS

2.1 Cases and Controls

The patients as *cases* with CA were selected from the Hungarian Congenital Abnormality Registry (HCAR) [10]. However, only cases reported to the HCAR in the first 3 months after births were evaluated in the HCCSCA, the excluded 23% of cases from the material of the HCAR were affected mainly with mild CAs. In addition cases with CA-syndromes caused by gene mutations or chromosomal aberrations with preconception origin were also excluded [9].

The so-called population controls were defined as newborn infants without CA and this sample represented the Hungarian newborn population. The source of these newborns was the National Birth Registry of the Central Statistical Office because their co-workers matched two newborns to each case on the basis of case lists for each quarter of the years of the HCAR. There were three matching criteria: sex, birth year and week and parents' district of residence. If controls were twins, only one of these twin-pairs was randomly selected for the HCCSCA

2.2 Evaluation of Birth Outcomes and Maternal Socio-Demographic Variables

Maternal age and birth order data were known in the HCAR. In addition, a letter with a printed informed consent included was mailed to the address of the mothers of the cases and controls immediately after their selection for the HCCSCA and they were requested to send us back within 4 weeks the prenatal maternity logbook (prenatal care was mandatory for pregnant women in Hungary), the discharge summary of delivery (practically all deliveries took place in hospitals, and attended by obstetricians) and every medical record concerning their child's CAs These documents were sent back within four weeks. The mean ± S.D. time elapsed between the end of pregnancy and return of the "information package" (including logbook, discharge summary, and informed consent) in our prepaid envelope was 3.5±2.1 and 5.2±2.9 months in cases and population controls, respectively.

In addition, regional district nurses were asked to visit all mothers of cases who did not respond within the stipulated time frame, in order to evaluate the available medical documents. Unfortunately district nurses could visit only 200 non-respondent and 600 respondent control mothers as part of two validation studies, because the ethics committee considered this follow-up to be disturbing for the parents of healthy children [9].

The data of maternal age and birth order were cross checked with the discharge summary of delivery, while both, the data of pregnancy order and the employment status (sensitive indicator of maternal socio-economic status) were evaluated on the basis of prenatal maternity logbook and discharge summary of delivery. The gestational age was calculated from the first day of the last menstrual period. Low birth weight was defined as birth weight less than 2500gram, and preterm births as births with less than 37 completed gestation weeks.

The necessary birth outcomes and maternal data were available for 96.3% of cases (84.4% from replies and 11.9% from visits) and 83.0% of controls (81.3% from replies and 1.7% from visits). The signed informed consent was sent back by 98% of mothers. Personal identifiers were deleted from the record of the remaining 2%.

As the data collection method was changed in 1997 (after the retirement of the last author of this paper), and as recent data have not been validated at the time of this analysis, only the 17 year span dataset of the HCCSCA, from 1980 through1996 was evaluated.

2.3 Study Design of Cases with SVC

The major evaluation problem of CHD was that CA cases were usually reported to the HCAR immediately after birth, and about 50% of cases with CHD were reported as unspecified CHD, because the exact diagnosis of CHD needed further time consuming

examinations. In fact, the medical data of cases with CA were available to the HCCSCA 3.5±2.1 months after births thus we were able to get specified CHD diagnoses in further 20% of cases. However, the remaining, i.e. 30% of CHD cases had no specified diagnoses in the HCCSCA. As most cases with CHD were cared or had surgical intervention in the pediatric cardiologic institutions in Hungary, one of us (M. Cs-Sz.) visited these cardiologic in- and outpatients clinics in 2008 in order to review the medical records of cases with CHD registered in the HCCSCA from 1980 through1996, check (and correct, if necessary) the previous CHD diagnosis and translate the unspecified CHD into specified diagnoses of CHD. Several new cases with CHD were found in the cardiologic clinics records, but as these patients had not been included data in the HCAR and HCCSCA, they were not evaluated. If cases were not found in the records of pediatric cardiologic institutions, we had a correspondence with their mothers, from 2009 through 2010, in order to clarify the fate and/or diagnosis of those cases. However, if the cases were not found, the diagnosis was not confirmed, the diagnosis of CHD was not specified based on autopsy or surgical documents or the mothers refused to collaborate, the cases were excluded from the study, in 2011.

SVC, also referred as univentricular heart was characterized by cases whose entire atrial blood flow was carried directly through the left and/or right atrioventricular valves into a single ventricular chamber. This anatomic structure explains the other names of this CHD-entity such as common ventricle or cor triloculare biatriatum. However, the phenotypic manifestation of SVC is heterogeneous [11-13]. SVC is associated with tricuspid or mitral atresia, and 3 subtypes are differentiated: SVC with normally related great vessels (65%), SVC with d-transposition of the great arteries (30%) and SVC with l-transposition of the great arteries.

Cases with syndromic SVC due to major mutant genes or chromosomal aberrations, as well as cases with multiple CAs including SVC were excluded from the study. Thus only the so-called isolated SVC cases with confirmed autopsy report diagnosis and/or intraoperative diagnosis with appropriate medical documentation were evaluated.

The development of atrioventricular canal occur between 26th and 35th postconception days, i.e. 40th and 49th gestational days, thus the critical period of SVC is in the second gestational month [14].

2.4 Statistical Analysis

The GNU R 2.14, RStudio 0.97 version (Alfréd Rényi Institute of Mathematics, Hungarian Academy of Sciences, Budapest, Hungary) software was used for the statistical analysis. The groups of maternal age, birth/pregnancy order, marital and employment status of mothers were evaluated by chi square test while the mean maternal age, birth/pregnancy order, gestational age and birth weight were evaluated by Student t test. In order to compare the rate of twins, preterm birth and low birthweight between cases and controls, we estimated the relative risk, *i.e.* odds ratio (OR), with 95% confidence interval (CI), by unconditional logistic regression model. As confounders we included maternal age, birth order (parity) and employment status of mothers.

3. RESULTS

Our data set included 76 live-born cases with SVC, 119 matched controls and 38,151 population controls without CA. As the data matched and population controls did not show any significant variable difference, we herein present only population controls data (here forth mentioned as controls). Of 76 cases, 40 (52.6%) were male, thus sex ratio was similar to the Hungarian newborn population (51.3%) sex ratio.

Main maternal variables are shown in Table 1. The mean maternal age was similar between groups (p = 0.362) though the proportion of mothers over 30 years was larger in the case group mothers. The birth order was significantly greater in the case group (p=0.044) due to the larger proportion of pregnant women with 3 or more previous births in the case group. Both the mean and distribution of pregnancy order (i.e. live- and stillbirth, plus miscarriages; ectopic pregnancies and elective termination of pregnancies were not recorded) was higher in the mothers of cases than in the mothers of controls (p=0.05). The mean pregnancy order was 0.4 inferior in the case group. This doubled figure may indicate a higher rate of miscarriages in the previous pregnancies of case mothers.

Table 1. Obstetrical and employment variables of SVC cases and control mothers

Variables	Case mothers (N=76)	Control mothers (N=38,151)	Comparison (p value)
Maternal age			
< 19			
20 – 29			0.090*
30 <			
Mean ± SD			
	26.1±5.6	25.5±4.9	0.362
Birth order			
1	31 (40.8)	18,209 (47.7)	
2	26 (34.2)	14,283 (37.4)	0.044*
3 or more	19 (25.0)	5,659 (14.8)	
Mean ± S.D.	1.9±1.0	1.7±0.9	0.086
Pregnancy order			
1	24 (31.6)	16,320 (42.8)	
2	20 (26.3)	13,443 (35.2)	0.0001*
3 or more	32 (42.1)	8,388 (22.0)	
Mean, S.D.	2.3±1.2	1.9±1.2	0.005
Categorical	.		
Unmarried	4 (5.3)	1,472 (3.9)	0.530
Employment status			
Professional	5 (6.6)	4,423 (11.6)	
Managerial	17 (22.4)	10,265 (26.9)	
Skilled worker	25 (32.9	11,908 (31.2)	0.110*
Semiskilled worker	10 (13.2)	6,161 (16.1)	
Unskilled worker	7 (9.2)	2,187 (5.7)	
Housewife	10 (13.2)	2,354 (6.2)	
Others	2 (2.6)	853 (2.2)	

**regarding the distribution of groups*

Table 2. Live-birth outcomes of SVC and control cases

Live-birth outcome	Cases (N=76)		Controls (N=38,151)		Comparison	Singleton cases (N = 72)		Singleton controls (N = 37,741)		Comparison
Quantitative	Mean	S.D.	Mean	S.D.	p=	Mean	S.D.	Mean	S.D.	p=
Gestational age (wk)*	39.3	2.4	39.4	2.1	.98	39.3	2.4	39.4	2.0	.98
Birthweight (g)**	3,050	568	3,276	512	.01	3,090	549	3,282	506	.01
Categorical	No.	%	No.	%	OR (95% CI)	No.	%	No.	%	OR (95% CI)
Twins*	4	5.3	386	1.0	5.11 (1.55-12.40)	0	0.0	0	0.0	- -
Preterm birth*	8	10.5	3,496	9.2	1.01 (0.44-1.99)	8	11.1	3,382	9.0	1.09 (0.47-2.16)
Low birthweight**	14	18.4	2,167	5.7	4.84 (2.23-9.71)	12	16.7	2,018	5.3	4.15 (1.78-8.81)

**Adjusted for sex and parity (birth order); ** Adjusted for sex, birth order, and gestational age; Bold numbers represent significant statistical differences*

Table 3. Live-birth outcomes of male and female singleton SVC and controls

Live-birth outcomes	Male cases (N=38)		Male controls (N=24,551)		Comparison	Female cases (N = 34)		Female controls (N = 13,190)		Comparison
Quantitative	Mean	S.D.	Mean	S.D.	p=	Mean	S.D.	Mean	S.D	p=
Gestational age (wk)*	39.0	2.4	39.4	2.0	.25	39.6	2.4	39.3	2.1	.25
Birthweight (g)**	3,136	590	3,300	508	.06	3,038	504	3,194	489	.005
Categorical	No.	%	No.	%	OR (95% CI)	No.	%	No.	%	OR (95% CI)
Preterm birth	5	13.2	2,000	8.1	1.51 (0.51-3.58)	3	8.8	1,382	10.5	0.74 (0.18-2.10)
Low birthweight**	7	18.4	1,155	4.7	5.15 (1.50-14.89)	5	14.7	863	6.5	3.30 (0.93-9.36)

**Adjusted for the age and parity (birth order); ** Adjusted for the age, parity (birth order), and gestational age of newborns; Bold numbers show significant association*

The intergroup rate of unmarried mothers was similar. The proportion of professional and managerial mothers as indicator of higher socioeconomic status was smaller in the case group (29.0% *vs* 38.5%) while the proportion of semi- and unskilled workers, as well as housewives was larger in case mothers (35.6% *vs* 28.3%)but this difference was not statistically significant (p=0.110).

The live-birth outcomes of both groups are shown in Table 2. The rate of twins was significantly higher in the SVC group. Of 4 twins, 2 were males, but the zygosity of them was not known.

The mean gestational age was 0.1 wk shorter in SVC cases. This finding was in agreement with the somewhat (1.2 fold) but not significantly higher rate of preterm births in the SVC group. However, the mean birth weight of SVC cases was 226 g smaller than the in the control group, and was associated with a 3.2 fold higher rate of low birthweight in the SVC group. Of 14 low birthweight cases, 7 (50.0%) were small for gestational age (i.e., 36th gestational week or more), while of 2,167 controls, 884 (40.7%) were SGA (OR with 95% CI: 1.55, 0.52-4.59). The authors stated previously that only the matched controls would be discussed! The higher number of twins in the SVC group did not seem to affect these findings for in singleton cases the preterm birth rate and the low birthweight rate were 1.4 and 3.2 fold higher, than in the singleton controls (Table 2).

Live birth outcomes of male and female singleton cases and controls are included in Table 3 above. The mean gestational age was 0.4 wk shorter in male cases than in male controls, but 0.3 wk longer in female cases than in female controls. The rate of preterm births was in agreement with gestational age, and was 1.6 fold higher in male cases but 0.8 fold lower in female cases as compared to their same sex controls. However, albeit their longer gestational age, females were 156 g less heavy than their controls, thus bearing a significantly lower gestational age specific birth weight. The mean birth weight was 164g less in male cases than in male controls.

4. DISCUSSION

The strengths of our study are the large data set of the HCCSCA including 76 cases of SVC and 38,151 population controls without CA, in the ethnically homogeneous Hungarian (Caucasian) population. The CHD-diagnoses were scrutinized through parents written reporting and available medical records obtained from cardiologic institutes and/or autopsy reports were included to the study. In addition, syndromic SVC cases were excluded.

The sex ratio of cases with SVC did not deviate from the sex ratio of Hungarian newborn population. The rate of twins was higher in our study (5.3%) and in the data set of Metropolitan Atlanta Congenital Defects Program (MACDP) (4.9%) [2]. Unfortunately, our data are not appropriate for the differentiation of mono- and dizygotic twins.

The mean birth weight was smaller in SVC cases, similarly to the data of to the MACDP findings (2,781 vs. 3,262g).But their data showed a shorter gestational age as well (36.5 vs. 38.8 wk) [2]. In our study, only male cases had a shorter gestational age, thus the sex seems to play an important role, although this finding was not supported by the MACDP study [2]. The mean birth weight was lower in both sexes, and the fetal hemodynamic effect of the SVC diagnosis in the fetuses may be the explanation [15]. On the other hand, as an association of some gene polymorphisms with fetal growth and birthweight was shown [16],

intrauterine growth restriction and SVC may also have a common route as two developmental errors.

The finding that the case mothers were not older then the control group ones, is in agreement with the MACDP [2]. An important finding of our study is the higher rate of pregnancy order in the SVC group because it suggests their mothers had higher rate of previous miscarriages with. However, SVC is relatively rare, its birth prevalence is 0.5-1.4 per 100,000 livebirths [11,2].

However, some study weaknesses must be emphasized. As our previous validation study showed the low reliability of retrospective self-reported information regarding mother lifestyle [17], only family consensus based on the cross interview of family members living together was evaluated (this should be stated in methods). However, only 9 SVC case mothers were visited at home.

5. CONCLUSION

SVC cases had a higher rate of twinning and lower birth weight, their mothers were more multiparous with a higher rate of previous miscarriages.

ETHICAL APPROVAL

The Central Ethical Committee of the Hungarian Ministry of Health approved the revised protocol of the Hungarian Congenital Abnormality Registry including the method to obtain and store of personal data of cases affected with congenital abnormality on the basis of informed consent of their mothers (41 440/1969. IV/1). The revised protocol of the Hungarian Case-Control Surveillance of Congenital Abnormalities was approved by the Central Ethical Committee of the Hungarian Ministry of Health (333/1979, IX/8). However, we wanted to ask regional nurses to visit and to question all non-respondent mothers, but the Ethical Committee allowed it only in non-respondent case mothers because they considered this follow-up to be disturbing for the parents of healthy children, i.e. non-respondent control mothers. Thus only 200 non-respondent and 600 respondent control mothers were visited at home and questioned by regional nurses as a part of two validation studies.

COMPETING INTERESTS

Authors have declared that no competing interests exist.

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