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Congenital Heart Disease in Children Living Close to the Former Semipalatinsk Nuclear Test Site: Frequency, Structure, and Links with Connective Tissue Dysplasia

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Abstract

BACKGROUND: Congenital heart disease (CHD) is the most common serious congenital disorder. CHD is the leading cause of death in the 1st year of life. One of the factors influencing the incidence of CHD is collagen structural abnormalities such as connective tissue dysplasia (CTD).

AIM: The aim of the study was to study the prevalence of CHD and their subtypes, to determine the combination of CHD and CTD with minor cardiac abnormalities (MCA).

METHODS: A retrospective study on the prevalence of CHD in the Republic of Kazakhstan and Semey city and a case–control study in the pediatric clinic of the Medical University Hospital was conducted. With CHD, CTD, and healthy children were included in the study. Children of all groups were examined according to the methodology, which included a collection of medical and family history; clinical examination; and assessment of CHD severity. The collected data were then analyzed using SPSS software.

RESULTS: The prevalence of CHD in Semey was 6.9/1000 live births. Atrial septal defect and ventricular septal defect were the most common CHD subtypes. The phenotype was represented by the asthenic physique, joint hypermobility, ear anomalies, and scoliosis. MCAs were in children with CHD and CTD. Mitral valve prolapse and left ventricular false tendons were detected most frequently.

CONCLUSION: MCAs detected in children with CTD. CTD is a factor influencing the severity of CHD.

Introduction

Congenital malformation is one of the main subjects of modern pediatrics and genetics. The most common serious congenital disorders are congenital heart disease (CHD) [1]. Twenty-eight percent of all congenital malformations consist of CHD. CHDs are the leading of mortality in the 1st year of live [2]. The CHD can lead to disability, therefore requires significant economic resources for surgical correction and social assistance to children with CHD. According to the literature, the birth prevalence of CHD is 7–8/1000 live births. The cause of 3% of all newborn deaths is CHD and 46% of deaths from congenital malformations. About 18–25% of infants die within the 1st year, and 4% of surviving infants die within 16 years [3].

In the Republic of Kazakhstan (RK), the birth prevalence of CHD is 8–10/1000 live births. CHD is 1 of the most frequently diagnosed congenital disorders [4]. Industrial development and environmental pollution increase the birth prevalence with congenital malformations, including CHD. At present, a polygenic model of CHD has been accepted, of which 89% are caused by environmental factors [5]. Ionizing radiation plays a significant role. In total, 468 nuclear tests were performed at the Semipalatinsk nuclear test site before 1990 [6]. About 54% of the territory of East Kazakhstan was occupied by a nuclear test site. Semey city is located in East Kazakhstan and is recognized as a region of increased radiation risk [7]. The activities of the nuclear test site caused irreparable damage to the environment and led to an increase in morbidity and mortality. The study of the environment around the nuclear test site has been going on for over 25 years. However, the reasons for the increase in the prevalence of CHD in Semey city are not fully understood at the present time.

Other factors affecting the prevalence of CHD include abnormalities in collagen structure, which cause CTD in childhood [8]. This is due to the peculiarities of the morphogenesis of the connective tissue: Its participation in the development of the heart at all stages of ontogenesis [9], [10]. At the same time, the effect of CTD on the severity of CHD is not fully understood.

The treatment and prevention measures for reducing the birth rate of children with CHD have to base on epidemiological data and clinical studies. In the prenatal and post-natal periods, it is necessary to assess the influence of various factors on the development of CHD, including the connective tissue condition [11], [12].

The purpose of our study was the prevalence of CHD and CHD subtypes according to the official statistics of the RK, to assess the phenotypic features of CTD in children with CHD, and to determine the combination of CHD with minor cardiac abnormalities (MCA).

Methods

Experimental data collection was for the period 2009-2013 from "Health of the population of the RK and the activities of health-care organizations" [13]. The data included: Congenital anomalies (malformations), deformities and chromosomal anomalies, congenital anomalies (malformations) of the heart and circulatory system in children from 0 to 14 years classified by ICD-10 as Q00-99, and statistical reporting cards of the RK. A retrospective study of the prevalence of congenital anomalies (Q00-Q99) and CHD (Q20-Q28) for the 5th year in Semey city (324,492 population), East Kazakhstan province (1,393,964 residents), and the RK was studied.

The objects of the clinical examination were 248 children aged 5–14 years living in Semey city (84 children with CHD, 84 children with phenotypic signs of CTD, and 80 healthy children in the control group). From 1 to 14 years old were included in the study corresponding to the WHO recommendations "Standard World Populations" where the age interval of childhood from 0 to 14 years was defined [14]. But we divided children into subgroups according to morphofunctional growth traits: The first was 1–3 years (infancy), the second was 4–7 years (period of deciduous teeth), the third was 8–10 years (period of older childhood), and the fourth was 11–14 years (period of puberty) [15]. Thus, the following groups were formed: Group A-84 children (38 females and 46 males) with CHD. Group B-84 children (36 females and 48 males) with CTD and control Group C-80 children (40 females and 40 males) without visible pathology. Children of all groups were examined by the following methodology in the University Hospital of Semey Medical University (SMU), including:

Medical and family history;

Clinical examination;

Assessment of CHD and CTD severity.

Diagnosis of CTD in children was performed using a specially designed questionnaire "Phenotypic and visceral signs of connective tissue dysplasia." We included into the questionnaire the phenotypic table of Glesby and Pyeritz (1989) and other frequently used items [16]. The questionnaires included 15 phenotypic features characteristic of CTD. We were also interested in visceral manifestations of CTD, such as MCA. EchoCG was used to detect MCA and CHD;

Instrumental examination: EchoCG was performed on Toshiba Device Vivid (Japan). The diagnosis of cardiac pathology included the following: CHD and MCA, such as mitral valve prolapse (MVP), left ventricular false tendons (LVFTs), functional systolic murmurs, cardiac arrhythmias, and incomplete right bundle branch block (IRBBB). The diagnosis of CHD was confirmed by history of disease, ECG and EchoCG findings.

Statistical analyses were done in SPSS software version 20.0 for Windows to calculate relative values and the fit coefficient ($\chi 2$). The incidence rate for the period 2009–2013 was calculated to rank from minimum to maximum. Results were presented as non-standardized mean ratios with 95% CI. For all statistical criteria, the error was 0.05. The study was approved by the SMU Ethics Committee (no. 2. 11/13/2017).

Results

We analyzed the statistical summary of the Ministry of Healthcare of the RK on the prevalence of congenital malformation (CM) and CHD in the RK and the Semey city.

Semey city is a territorial unit of East Kazakhstan. Therefore, the analysis of the prevalence of CM and CHD was carried out in East Kazakhstan too. It was a retrospective study in 5 years from 2009 to 2013. We studied the prevalence of CM in RK, East Kazakhstan and Semey city (Table 1).

Table 1: Prevalence of first-time registered congenital malformations per 100,000 population

Area	2009	2010	2011	2012	2013
Republic of Kazakhstan	205.7	208.3	221.8	225.1	215.6
East Kazakhstan	107.9	122.4	114.0	102.3	97.7
Semey city	92.5	133.9	122.4	90.0	90.6

The next step was to analyze the statistics of the total number of live births in the RK, East Kazakhstan and Semey city (Table 2). From 2009 to 2013, 29,672 were born in Semey city. The prevalence of live births in 2009-6234 infants (17.6/1000 live births), in 2010-6031 infants (16.7/1,000 live births), in 2011-5561 infants (16.8/1000 live births), 2012-5922 infants (17.8/1,000

Table 2: Prevalence of live births per 1000 population

Area	2009	2010	2011	2012	2013
Republic of Kazakhstan	22.45	22.52	22.52	22.69	23.73
East Kazakhstan	16.76	16.81	16.37	16.67	16.43
Semey city	17.56	16.67	16.8	17.75	17.6

live births), and 2013-5924 infants (17.6/1000 live births). Table 2 shows that the prevalence of live births in Semey city was higher than in the East Kazakhstan.

Table 3 shows that in Semey city from 2009 to 2013 the total number of CM in children from 0 to 14 years old was 1091 cases including 336 (30.8%) cases of congenital anomalies of heart and circulatory system (CAHCS). Analysis the incidence of CAHCS in Semey city showed that in 2010, 2011, and 2012 that the incidence was higher than in 2009 and 2013.

Table 3: Prevalence of congenital malformations, congenital anomalies of the heart, and circulatory system from 0 to 14 years old, per 10,000 live births

ICD-10	2009	2010	2011	2012	2013
Q00-Q99 Congenital malformations	2.49 (2.12–2.86)	4.04 (3.56–4.52)	3.80 (3.32–4.04)	2.82 (2.43–3.21)	2.96 (2.56–3.36)
Q20-Q28 Congenital anomalies of heart and circulatory system	0.89 (0.65–1.13)	1.33 (1.05–1.61)	1.01 (0.77–1.13)	1.02 (0.76–1.13)	0.69 (0.51–0.88)

The prevalence of CHD subtypes was also studied. During the study period, there were 84 CHD cases: in 2009-18; in 2010-22; in 2011-19; in 2012-17; and in 2013-20. CHD subtypes ASD (Q21.1), VSD (Q21.0) prevail in 18 children and 16 children, respectively. TOF (Q21.3) was present in nine children, PDA (Q25.0) in eight children, TGA (Q20.3) in eight children, PFO in six children, VSPA (Q22.1) in five children, BAV (Q23.1), CoA (Q25.1), CAD (Q23.1) in four cases, SV (Q20.4), and Taussig-Bing anomaly (Q20.1) in one case (Table 4).

Table 4: Profile of congenital heart disease in Semey city

Subtypes	n	%	95% CI
Atrial septal defect (ASD)	18	21.4	13.5–32.0
Ventricular septal defect (VSD)	16	19.0	11.6–29.4
Tetralogy of Fallot (TOF)	9	10.7	5.3–19.8
Patent ductus arteriosus (PDA)	8	9.5	4.5–18.4
Transposition of the great arteries (TGA)	8	9.5	4.5–18.4
Patent foramen ovale (PFO)	6	7.1	2.9–15.5
Valvular stenosis of the pulmonary artery (VSPA)	5	5.9	2.2–14.0
Bicuspid aortic valve (BAV)	4	4.7	1.5–12.4
Coarctation of the aorta (CoA)	4	4.7	1.5–12.4
Combined aortal defect (CAD)	4	4.7	1.5–12.4
Single ventricle (SV)	1	1.2	0.1–7.3
The anomaly Taussig-Bing	1	1.2	0.1–7.3
Total	84	100	-

We observed phenotypic signs in children with CHD (Group A), CTD (Group B), and the control Group C (children without CHD and CTD) (Table 5). Group A children had 14 phenotypic signs, Group B had 15 phenotypic signs, and Control Group C had 11 phenotypic signs. Analysis of phenotypic signs indicates statistically significant correlation in children of all groups for the following: Asthenic physique, hypermobility of joints, ear anomalies, and scoliosis. In both groups (A and B), the most explicit were the chest deformity, arachnodactyly, flat feet, hypotonia. The following phenotypic signs: Hernias, increased skin extensibility, and visible veins showed no statistical significance ($\chi 2$=2.0; 4.9; and 3.6, respectively, p>0.05).

Table 5: Phenotypes in the study groups

Phenotypic signs	A n (%)	B n (%)	C n (%)	χ^2
Asthenic physique	72 (85.7)	47 (56.0)	17 (21.3)	68.8
Chest deformity	50 (59.5)	15 (17.9)	0	79.6
Arachnodactyly	29 (34.5)	13 (15.4)	1 (1.3)	32.0
Dolichostenomelia	20 (23.8)	14 (16.7)	5 (6.3)	9.6
Scoliosis	31 (36.9)	31 (36.9)	6 (6.5)	23.5
Joint hypermobility	68 (80.9)	73 (86.9)	16 (20.0)	100.1
Flat feet	26 (30.9)	28 (33.3)	13 (16.3)	7.1
Ear anomalies	69 (82.1)	29 (34.5)	10 (12.5)	85.0
Increased skin extensibility	3 (3.5)	9 (10.7)	3 (3.8)	4.9*
Ecchymosis, petechiae, epistaxis	11 (13.1)	19 (22.6)	7 (8.8)	6.5
Visible veins	3 (3.6)	8 (7.1)	3 (3.8)	3.6*
Changes in the bite	30 (35.71)	16 (19.0)	30 (37.5)	8.1
Gothic palate	9 (10.71)	7 (8.33)	0	8.5
Umbilical/inguinal/scrotal hernias	0	1 (0.1)	0	2.0*
Hypotonia	15 (17.9)	13 (15.5)	0	15.3

*–p > 0.05 (n' = 2). Group A - 84 children with CHD, Group B - 84 children with CTD, Group C - 80 control.

At present, there is no consensus on the clinical significance of MCAs, many of which have unstable characteristics related to child growth. MCAs are often detected by EchoCG in children and adolescents. Tables 6 and 7 show EchoCG findings in children with CHD and CTD at different ages. MCAs are assessed based on existing or non-existing abnormalities.

As shown Table 6, MCAs are also found in children with CHD. The incidence of MVP ranges from 9.5% to 13.1% and increases with the age of children. Of 84 children with CHD, 36 children (42.9%) had a MVP. Rhythm disturbances are registered with RBBB. In our study, 47 (55.9%) children had this pathology. RBBB was more common in young children (1-3 years) - 15.5%, and in adolescents (11-14 years) - 30.9%. In children aged 4–7 and 8–10 years, RBBB was less common, but often combined with ventricular hypertrophy. Violation of rhythm and conductivity of heart was registered in each age group and in total was in 52 children (61.9%), but the greatest cases were in younger children. LVFT was more frequently registered in the younger group (25.0%) compared with the other age groups (8.3%, 4.8%, and 8.3%, respectively). LVNC had a similar distribution by age group. Thus, it was found that MCA are closely associated with CHD. It is known that external phenotypic traits and internal visceral traits are required to deliver the diagnosis of CTD [17]. Therefore, we analyzed MCA in children with CTD (Table 7).

As shown in Table 7, MCAs occur in children of all age groups. The high frequency of such stigmata as PMC (52.3%), LVFT (55.9%) is due to intensified developmental processes, predominantly in the connective tissue stroma of the heart. Regarding age, the highest percentage of the presenting MCA was in the 8–10 age groups, which seems to be related to the activation of the neuroendocrine system for this age.

Discussion

CHDs are the most common cause of major congenital anomalies, representing a major global health problem. CHD, by definition, is present from birth [18]. The birth prevalence of CHD varies widely among countries. Europe is reported to have the

Table 6: Age-related features of minor cardiac abnormalities in children with congenital heart disease

Minor cardiac abnormalities	1–3 age n = 22	4–7 age n = 24	8–10 age n = 12	11–14 age n = 26	Total
Mitral valve prolapse (MVP), n	8 (9.5)	6 (7.1)	11 (13.1)	11 (13.1)	36 (42.9)
Left ventricular noncompaction (LVNC), n	13 (15.5)	7 (8.3)	4 (4.8)	7 (8.3)	31 (36.9)
Patent foramen ovale (PFO), n	22 (26.2)	15 (17.9)	7 (8.3)	8 (9.5)	52 (61.9)
Left ventricular false tendons (LVFT), n	21 (25.0)	4 (4.8)	10 (11.9)	4 (4.8)	39 (46.4)
Violation of rhythm and conductivity of heart, n	13 (15.5)	17 (20.2)	11 (13.1)	11 (13.1)	52 (61.9)
Incomplete Right Bundle Branch Block (IRBBB), n	13 (15.5)	7 (8.3)	1 (1.2)	26 (30.9)	47 (55.9)
Left ventricular hypertrophy, n	4 (4.8)	10 (11.9)	8 (9.5)	6 (7.1)	26 (30.9)
Right ventricular hypertrophy, n	1 (1.2)	4 (4.8)	3 (3.5)	0	8 (9.5)

second highest birth prevalence of CHD and the rate is significantly higher than in North America (8.2/1,000 live births vs 6.9/1,000 live births). Geographic differences are important. The overall prevalence of CHD has been reported to be significantly higher in Asia compared to all other continents (9.3/1000 live births) [19]. Indian authors found the prevalence of CHD in the general population was 6.4/1000 live births in children under 18 years of age [20]. In Taiwan, the prevalence of CHD was 9.2/1000 live births [21]. In our study, CHD birth prevalence in Semey city ranged from 6.9 to 13.3/1000 live births (Table 3), which agrees with the official data in the RK (from 8.0 to 10.0/1000 live births).

We also studied the data on CHD incidence by its subtypes. CHD were divided into 12 subtypes. The largest contributors to the spectrum of CHD in children from Semey city were VSD, ASD, TOF, PDA, and TGA which were detected in 9.5–21.4% of all CHD cases (Table 4). According to systematic review of Linde *et al*., the most common subtypes reported worldwide (per 1000 live births) are VSD, 2.62; ASD, 1.64; PDA, 0.87; and PS, 0.50 [19]. In another study (Wu *et al*.), VSD and ASD were the most common subtype of CHD with an incidence of 5.29/1000 and accounted for about 29.6% of all CHD cases [4]. In our study, ASD and VSD were also the most common subtypes of CHD and accounted for 19.0% and 21.4%, respectively.

EchoCG is a method to study valve morphology and the fibrous skeleton of the heart *in vivo*. EchoCG also diagnoses small anatomical changes in the heart. Now MCA is inherited structural and metabolic changes of heart valves and/or fibrous skeleton, including trunk vessels, without serious hemodynamic and clinical abnormalities.

We performed a bibliographic search in PubMed and found that the definition of MCA is not used in publications in English. There are publications devoted to specific cardiac abnormalities and their clinical significance [22]. A search for publications in Russian gave us a sufficient number of publications on the connection between connective tissue dysplasia and MCA. It was shown [23] that the more changes in the stroma and valves of the heart, the more often signs of connective tissue dysplasia (phenotype) are revealed in such patients. This gave us grounds to consider MCA as a manifestation of CTD.

In our study in children with CTD, MACs were as follows: MVP, LVNC, PFO, LVFTs, IRBBB. MVP is a common valve pathology with a spectrum of disease from isolated prolapse to myxomatous. Myxomatous form is a separate disease [24]. Isolated MVP, which refers to MCA, has the following features on EchoCG: Valve prolapse (<3 mm) and mitral regurgitation (not more than 1 degree) [23]. However, diagnosed isolated MVP can progress and become a clinical heart syndrome. IRBBB, PFO can be associated with some serious conditions as well. In our study, MVP was in all age groups of children with CTD in 52.3% of cases and LVFTs in 55.9% of cases.

Thus, dysplasia is a heterogeneous, multifactorial diseases of connective tissue united into phenotypes based on the commonality of external and/or visceral features [24], [25]. Diagnosis of CTD should start with exclusion of genetic defects of connective tissue (associated with autosomal abnormalities), such as Down's disease, trisomy chromosome eight syndrome, and Klinefelter syndrome [26]. When genetic is excluded, the CTD is based on the identification of ≥6 small external (phenotypes) and/or visceral manifestations involving ≥3 different organs from different systems [17], [27].

In our study, the characteristic phenotypes were present in the group of children with CHD and with CTD, and the visceral manifestations were MCA. We analyzed the prevalence of CHD and tried to link CTD to CHD. The results showed that structural changes in connective tissue affect the severity of CHD.

Table 7: Age-related features of minor cardiac abnormalities in children with congenital heart disease

minor cardiac abnormalities	1–3 age n = 10	4–7 age n = 18	8–10 age n = 24	11–14 age n = 32	Total
Mitral valve prolapse (MVP), n	7 (8.3)	9 (10.7)	22 (26.2)	6 (7.1)	44 (52.3)
Left ventricular noncompaction (LVNC), n	4 (4.8)	12 (14.3)	6 (7.1)	5 (6.0)	27 (32.4)
Patent foramen ovale (PFO), n	5 (6.0)	3 (3.5)	8 (9.5)	3 (3.5)	19 (22.6)
Left ventricular false tendons (LVFT), n	6 (7.1)	10 (11.9)	19 (22.6)	12 (14.3)	47 (55.9)
Violation of rhythm and conductivity of heart, n	2 (2.4)	9 (10.7)	10 (11.9)	6 (7.1)	27 (32.2)
Incomplete Right Bundle Branch Block (IRBBB), n	4 (4.8)	4 (4.8)	11 (13.1)	3 (3.5)	22 (26.2)
Left ventricular hypertrophy, n	5 (6.0)	3 (3.5)	12 (14.3)	6 (7.1)	26 (31)
Right ventricular hypertrophy, n	0	4 (4.8)	0	2 (2.4)	6 (7.1)

Conclusions

The prevalence of CHD was 30.8% of congenital malformations. ASD and VSD were the most common among CHD subtypes. We also studied phenotypes in children with CHD and CTD and found similarities in phenotypic signs in children of these groups. The prevalence of MCA was studied, most of which have unstable characteristics associated with child growth. MCAs detected in children with CTD. CTD is a factor influencing the severity of CHD.

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Author Contributions

Conceptualization and methodology Madina Madiyeva; validation, formal analysis, data curation, Tamara Rymbaeva; writing-original draft preparation, writing-review and editing, funding acquisition, Madina Madiyeva. All authors have read and agreed to the published version of the manuscript.

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