Congenital heart disease detection in Slovenia: Improvement potential of neonatal pulse oximetry screening

Diagnostika prirojenih srčnih napak v Sloveniji: Kaj bi lahko doprinesla uvedba presejanja s pulzno oksimetrijo

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Abstract

Introduction: Patients with major or critical congenital heart disease (CHD) require surgical treatment or interventional cardiac catheterization during the first year or 28 days of life, respectively. Currently, the detection of CHD in Slovenia relies on the prenatal ultrasound screening and physical examination of the newborn.

Aims: 1) To determine the incidence of major/critical CHD in Slovenia; 2) to determine the proportion of infants with late detection of major/critical CHD based on the existing clinical practice; and 3) to estimate the improvement in CHD detection with a nation-wide neonatal pulse oximetry screening programme.

Methods: We reviewed the documentation of all patients with major/critical CHD born in Slovenia in years 2007–2012. We determined whether the heart condition was detected: 1) on time – prenatally or prior to discharge from maternity ward; or 2) late – after discharge or at autopsy.

Results: Among 128,839 live-born babies, 293 were diagnosed with a major CHD (2.27/1000 live births, 95 % confidence interval (CI): 2.0–2.5/1000) and of those 150 with a critical CHD (1.16/1000 live births, 95 % CI: 1.0–1.4/1000). Late detection occurred in 17.7 % of patients with major and 10.9 % patients with critical CHD. Out of 15 late-detected patients with critical CHD, 14 had an obstructive left heart lesion. In 2 patients CHD was diagnosed after death.

Conclusions: Detection of CHD in Slovenia is satisfactory. However, in the observed period, 10.9 % of newborns with a critical CHD were discharged undiagnosed. A nation-wide pulse oximetry screening programme could improve pre-discharge CHD detection.

Izvleček

Uvod: Prirojene srčne napake (CHD) so najpogostejše prirojene napake organov in organskih sistemov. Pri polovici bolnikov so napake hemodinamsko pomembne, kar pomeni, da je potrebno kirurško ali kardiološko intervencijsko zdravljenje v prvem letu življenja. Podskupino predstavljajo bolniki s kritičnimi CHD, pri katerih je zdravljenje potrebno v prvih 28 dneh življenja. CHD ugotavljamo s kliničnim pregledom novorojenčka, pred rojstvom pa z ultrazvočnim pregledom plodovega srca. Kljub široki dostopnosti obeh preiskav ostane del bolnikov do odpusta iz porodnišnice neprepoznanih. Kot uspešna dopolnilna metoda za prepoznavanje novorojenčkov s CHD se je v zadnjih letih uveljavilo presejanje s pulzno oksimetrijo.

Namen raziskave: 1) ugotoviti incidenco prirojenih srčnih napak v Sloveniji, 2) ugotoviti delež bolnikov, ki ostanejo neprepoznani do odpusta iz porodnišnice, in 3) oceniti potencial za izboljšanje prepoznave CHD ob morebitni uvedbi presejanja s pulzno oksimetrijo na nacionalni ravni.

Metode: V raziskavo smo vključili otroke s hemodinamsko pomembnimi/kritičnimi CHD, rojenimi v Sloveniji v obdobju 2007–2012. Podatke smo pridobili iz različnih podatkovnih baz in osebnih kartotek bolnikov, vodenih v sklopu Univerzitetnega kliničnega centra Ljubljana, edinega centra za kardiokirurško in kardiološko intervencijsko obravnavno otrok s prirojenimi srčnimi napakami v Sloveniji. Za vsakega posameznega bolnika smo opredelili, ali je bila CHD razpoznana pravočasno (pred rojstvom oz. pred odpustom iz porodnišnice) ali pozno (po odpustu iz porodnišnice oz. po smrti).

Rezultati: V obravnavanem obdobju je bilo v Sloveniji rojenih 128.839 otrok. Pri 293 otrocih (2,27/1000) smo ugotovili hemodinamsko pomembno CHD, pri 150 od njih (1,16/1000) smo napako opredelili kot kritično. Med bolniki s hemodinamsko pomembnimi CHD je bilo pozno razpoznanih 17,7 %, med bolniki s kritičnimi CHD pa 10,8 % otrok. Od 15 bolnikov s pozno razpoznanimi kritičnimi CHD, jih je 14 imelo napake z obstrukcijo toka krvi v področju levostranskih srčnih struktur. Dva bolnika sta bila razpoznana šele po smrti.

Zaključki: Razpoznava novorojenčkov s hemodinamsko pomembnimi in kritičnimi CHD z ustaljenimi diagnostičnimi postopki, prenatalnim ultrazvočnim presejanjem in kliničnim pregledom novorojenčka je v Sloveniji dobra, še vedno pa ostaja ob odpustu iz porodnišnic približno desetina bolnikov s kritičnimi CHD neprepoznanih. Delež pozno razpoznanih bolnikov s kritičnimi CHD bi lahko zmanjšali z uvedbo presejalnega testiranja novorojenčkov s pulzno oksimetrijo.

1. Introduction

Congenital heart disease (CHD) is the most common group of congenital malformations and accounts for more than one third of major congenital anomalies diagnosed prenatally or in infancy (1). The incidence of CHD is approximately 6–7/1000 newborns (2,3). Half of the patients have minor CHD that does not require treatment, or can be corrected later on in life. The remainder require cardiac surgery or interventional cardiac catheterization in the first year of life. Early diagnosis is particularly important in patients with duct-dependent lesions in which closure of the ductus arteriosus can result in acute cardiovascular collapse, acidosis, and death (4-6). Despite the improvement in diagnostics and treatment of CHD in the last few decades, CHD still cause significant morbidity and mortality, accounting for more than one third of deaths in children with congenital anomalies in the first year of life (7).

Screening strategies to detect CHD include prenatal ultrasound and physical examination of the newborns. However, using just these two diagnostic options, a sizeable proportion of patients remains undetected before discharge from the maternity units (8-10). Neonatal pulse oximetry screening reduces this diagnostic gap and helps identify infants with critical CHD before they present with acute cardiovascular collapse (11–14).

The aims of our study were to: 1) determine the incidence of major and critical CHD in Slovenia; 2) determine the proportion of infants with late detection of major/critical CHD based on existing clinical practice; and 3) estimate the improvement in CHD detection with a nation-wide neonatal pulse oximetry screening programme.

2. Methods

The study group consisted of all live-born infants with major/critical CHD in Slovenia from January 1, 2007, through December 31, 2012. Patients were identified by reviewing and cross-checking data from four different databases: 1) patients referred for surgical treatment of

CHD; 2) patients referred for interventional cardiac catheterization for CHD; 3) patients with prenatally diagnosed CHD; and 4) Death Registry of the National Institute of Public Health.

Major and critical CHD were defined as requiring surgical treatment or interventional cardiac catheterization or causing death during the first year or first four weeks of life, respectively. Data were obtained from labour and delivery records and personal medical records at the University Medical Centre Ljubljana (UMCL). All patients, except those who died before referral to UMCL, underwent a detailed echocardiographic examination with the assessment of cardiac morphology and function at UMCL, a single tertiary referral centre for children with CHD serving a population of 2 million in Slovenia. The echocardiograms were performed using the Aloka Prosound SSD-5500, Aloka α 10 and Aloka α 7 ultrasound systems (Aloka Co. Ltd., Tokyo, Japan). Congenital heart defects were classified according to the standard anatomic nomenclature that assigns priority to morphologically dominant traits. Patients with isolated patent ductus arteriosus (PDA) that was a consequence of prematurity were excluded from the study.

By reviewing the documentation, we additionally determined whether the diagnosis of CHD for each patient was established: 1) prenatally; 2) prior to discharge from the maternity ward; 3) after discharge from the maternity ward; and 4) at autopsy. We considered patients that were diagnosed prenatally or prior to discharge from the maternity ward as detected on time, while those diagnosed after discharge or at autopsy as detected late.

To objectively estimate the potential improvement in on-time detection of CHD with a nation-wide neonatal pulse oximetry screening programme, we excluded the following patients from further analyses: 1) with recognized or strongly suspected chromosomal aberrations at the first neonatal examination (25 patients); 2) with oesophageal atresia or diaphragmatic hernia (5 patients); 3) admitted to the neonatal intensive care unit due to prematurity (born at 33 gestational weeks or less, 7 patients); and/or 4) born at home (1 patient). We assumed that these patients would not be eligible for neonatal pulse oximetry screening since they would have had a detailed clinical examination and possibly echocardiography done solely on the basis of their primary condition. For obvious reasons, the patient that was born at home would also not be screened by pulse oximetry.

Statistical analyses were performed using MedCalc for Windows, version 16.4.3 (MedCalc Software, Ostend, Belgium). The confidence intervals for the incidence rates were calculated as suggested by Sahai and Khurshid (15). We used chi-square test to compare data with categorical outcomes.

3. Results

During the 6-year study period, there were 128,839 live-born babies in Slovenia (16). 293 were diagnosed with a major CHD, and among these 150 had critical CHD. Therefore, the incidence of major CHD in Slovenia was 2.27/1000 live births (95 % CI: 2.0–2.6/1000) and 1.16/1000 live births (95 % CI: 1.0–1.4/1000) for critical CHD. The incidence of specific major forms of CHD is presented in Table 1.

In our series, major CHD were more common in males than females. In years 2007–2012, 66,282 boys were born in Slovenia, of which 172 were diagnosed with major CHD (2.5/1000 live births,

Table 1: The incidence of specific forms of major and critical CHD in Slovenia from 2007–2012.

Live births n = 128839				
	Major CHD		Critical CHD only	
Defect type*	**n**	**n/10000 (95 % CI)**	**n**	**% of major CHD**
All	293	22.7 (20.2–25.5)	150	51.2
CoAo	59	4.5 (3.5–5.9)	48	81.4
VSD	58	4.5 (3.4–5.8)	1	1.7
d-TGA	32	2.5 (1.7–3.5)	32	100
ToF	26	2.0 (1.3–3.0)	5	19.2
AVSD	22	1.7 (1.1–2.6)	3	13.7
HLHS	19	1.4 (0.9–2.3)	19	100
AoSt	17	1.4 (0.8–2.1)	13	5.9
PA-VSD	9	0.7 (0.3–1.3)	6	66.7
PuSt	8	0.6 (0.3–1.2)	4	50
DORV	6	0.5 (0.2–1.0)	3	50
IAA	6	0.5 (0.2–1.0)	6	100
Truncus Arteriosus	5	0.4 (0.1–0.9)	0	0
Univentricular Heart	3	0.2 (0.05–0.7)	2	66.7
PA-IVS	3	0.2 (0.05–0.7)	3	100
PDA	3	0.2 (0.05–0.7)	0	0
TAPVD	3	0.2 (0.05–0.7)	2	66.7
Other†	14	1.1 (0.6–1.8)	3	21.4

**CoAo – coarctation of the aorta; VSD – ventricular septal defect; d-TGA – d-transposition of the great arteries; ToF – tetralogy of Fallot; AVSD – atrioventricular septal defect; HLHS – hypoplastic left heart syndrome; AoSt – aortic stenosis; PA-VSD – pulmonary atresia with ventricular septal defect; PuSt – pulmonary stenosis; DORV – double outlet right ventricle; IAA – interruption of the aortic arch; PA-IVS – pulmonary atresia with intact ventricular septum; PDA – patent ductus arteriosus; TAPVD – total anomalous pulmonary venous drainage*

†Absent pulmonary valve syndrome; anomalous left coronary artery originating from pulmonary artery (ALCAPA); aorto-left ventricular tunnel; aorto-pulmonary window; atrial septal defect type primum; atrial septal defect type secundum; congenitally corrected transposition of great arteries; double aortic arch; pulmonary veins stenoses; tricuspid valve atresia.

95 % CI: 2.2–3.0/1000). In the same time period, 62,557 girls were born, of which 121 had major CHD (1.9/1000, 95 % CI: 1.6–2.3/1000 live births). The difference is statistically significant (p = 0.01).

Chromosomal and genetic aberrations were detected in 41 patients (14.3 %) with major CHD. The type of the genetic defect and the form of CHD are presented in Table 2. One fifth of patients in our series were born prematurely, at a gestational age ≤ 37 weeks. The proportion of multiple birth pregnancies in patients with major CHD was significantly higher than in the general population (6.14 % vs. 3.49 %, p = 0.01).

Table 2: Chromosomal and genetic aberrations in patients with major CHD.

Aberration	Total (N)	Cardiac Defect Type*	n
Trisomy 21	24	AVSD	18
		VSD	6
Deletion 22q11.2	8	Absent PuV syndrome*	1
		IAA	1
		PA-VSD	2
		ToF	2
		Truncus Arteriosus	1
		VSD	1
Klinefelter Syndrome	2	PA-IVS	1
		CoAo	1
Trisomy 18	1	VSD	1
Turner Syndrome	1	CoAo	1
Triple X Syndrome	1	DORV	1
Charge Syndrome.	1	PuSt	1
Opitz Syndrome	1	VSD	1
Kabuki Syndrome	1	VSD	1
Subtelomeric Deletion	1	VSD	1
All	41		

**AVSD – atrioventricular septal defect; VSD – ventricular septal defect; absent PuV syndrome – absent pulmonary valve syndrome; IAA – interruption of the aortic arch; PA-VSD – pulmonary atresia with ventricular septal defect; ToF – tetralogy of Fallot; PA-IVS – pulmonary atresia with intact ventricular septum; CoAo – coarctation of the aorta; DORV – double outlet right ventricle; PuSt – pulmonary stenosis*

Table 3: Timing of detection of major and critical CHD.

	Major CHD n (%)	Critical CHD only n (%)
Prenatally	40 (15.7 %)	28 (20.3 %)
Prior to discharge	170 (66.6 %)	95 (68.8 %)
After discharge	43 (16.9 %)	13 (9.4 %)
Post mortem	2 (0.8 %)	2 (1.5 %)
All	255	138

As described in the Methods chapter of this article, we included 255 patients in the second part of the study, where we analysed the timing of detection of major/critical CHD. The general results are summarised in Table 3 and the specific results based on the major forms of CHD are presented in Table 4. The diagnosis of a major CHD was established after discharge or at autopsy for 45 of the 255 patients (17.5 %). Among 138 neonates with critical CHD 15 patients (10.9 %) were detected late, 13 of them after discharge from the maternity ward and the remaining two at autopsy (Table 5).

4. Discussion

To our knowledge, this is the first study that investigated the incidence of major and critical CHD in the Slovenian population. The reported incidence is in agreement with previously published series (11,13,17). The incidence would be approximately 21 % higher if all women in whom CHD had been detected prenatally would have decided to continue pregnancy (unpublished data).

The definition of major/critical CHD may exclude occasional patients with well-balanced complex CHD who might not need surgical treatment before one year of age and/or inappropriately includes patients with simple lesions who have had heart surgery performed within the first year of life. However, we believe that our definition allows satisfactory identification of those patients who could benefit most if their heart condition is detected on time. Not all heart defects are equally important and not all need to be treated during the first month/year of life. Atrial septal defects, for example, very rarely cause any clinical problems before adulthood and are most commonly scheduled for closure at the age of 4 to 6 years, even if detected in

Table 4: Timing of detection of major CHD by specific defect type.

Major CHD			
	On-time Detection	Late Detection	Total
Defect type*	**n (%)**	**n (%)**	**N**
CoA	39 (72.2 %)	15 (27.8 %)	54
VSD – All Types	39 (78 %)	11 (22 %)	50
d-TGA	32 (100 %)	-	32
ToF	22 (91.7 %)	2 (8.3 %)	24
HLHS	15 (83.3 %)	3 (16.7 %)	18
AoSt	14 (87.5 %)	2 (12.5 %)	16
PuSt	7 (87.5 %)	1 (12.5 %)	8
PA-VSD	6 (85.7 %)	1 (14.3 %)	7
DORV	6 (100 %)	-	6
AVSD	5 (100 %)	-	5
IAA	5 (100 %)	-	5
Truncus Arteriosus	4 (80 %)	1 (20 %)	5
Univentricular Heart	3 (100 %)	-	3
TAPVD	2 (66.7 %)	1 (33.3 %)	3
PDA	2 (66.7 %)	1 (33.3 %)	3
Other†	9 (56.3 %)	7 (43.7 %)	16
Total	210 (82.3 %)	45 (17.7 %)	255

**CoAo – coarctation of the aorta; VSD – ventricular septal defect; d-TGA – d- transposition of great arteries; ToF – tetralogy of Fallot; HLHS – hypoplastic left heart syndrome; AoSt – aortic stenosis; PuSt – pulmonary stenosis; PA-VSD – pulmonary atresia with ventricular septal defect; DORV – double outlet right ventricle; AVSD – atrioventricular septal defect; IAA – interruption of the aortic arch; TAPVD – total anomalous pulmonary venous drainage; PDA – patent ductus arteriosus*
†Absent pulmonary valve syndrome; anomalous left coronary artery originating from pulmonary artery (ALCAPA); aorto-left ventricular tunnel; aorto-pulmonary window; atrial septal defect type primum; atrial septal defect type secundum; congenitally corrected transposition of the great arteries; double aortic arch; pulmonary atresia with intact ventricular septum; pulmonary veins stenoses; tricuspid valve atresia.

neonates. Another example is bicuspid aortic valve which might be only mildly stenotic at birth and does not need any intervention until a significant stenosis or regurgitation of the valve develops, which is usually well beyond infancy and childhood. Some minor defects even close spontaneously or never need any medical attention. Based on our data, approximately 50 babies per year need cardiac surgery or interventional cardiac catheterization during the first year of life in Slovenia, half of them during the first month.

Currently, the detection of CHD in Slovenia relies primarily on the prenatal mid-trimester ultrasound cardiac screening performed by gynaecologists and the neonatal clinical examination performed by paediatricians. The latter

Table 5: Timing of detection of critical CHD by specific defect type.

Critical CHD			
	On-time Detection	Late Detection	Total
Defect type*	**n (%)**	**n (%)**	**N**
CoAo	34 (79.1 %)	9 (20.9 %)	43
d-TGA	32 (100 %)	-	32
HLHS	15 (83.3 %)	3 (16.7 %)	18
AoSt	10 (83.3 %)	2 (16.7 %)	12
IAA	5 (100 %)	-	5
PA-VSD	4 (100 %)	-	4
ToF	4 (80 %)	1 (20 %)	5
PuSt	4 (100 %)	-	4
DORV	3 (100 %)	-	3
Other†	12 (100 %)	-	12
Total	123 (89.1 %)	15 (10.9 %)	138

**CoAo – coarctation of the aorta; d-TGA – d-transposition of great arteries; HLHS – hypoplastic left heart syndrome; AoSt – aortic stenosis; IAA – interruption of the aortic arch; PA-VSD – pulmonary atresia with ventricular septal defect; ToF – tetralogy of Fallot; PuSt – pulmonary stenosis; DORV – double outlet right ventricle*

†Aorto-left ventricular tunnel; atrioventricular septal defect; congenitally corrected transposition of great arteries; pulmonary atresia with intact ventricular septum; total anomalous pulmonary venous drainage, tricuspid valve atresia; univentricular heart.

includes the assessment of heart sounds and femoral pulses as well as inspection for cyanosis. If CHD is suspected, patients are referred to a foetal/paediatric cardiologist for further cardiac evaluation . Of particular importance is timely detection of critical, duct-dependent lesions in which closure of the ductus arteriosus may result in acute cardiovascular collapse and death (4,5,18). Our study demonstrates that currently 90 % of patients with critical CHD in Slovenia are detected either in utero or shortly after birth, before being discharged from the maternity ward. The pre-discharge detection rate in our series was higher than previously reported in UK, Sweden and USA, where it ranged from 70–82 % (8-11). This might be at least partly explained by longer average length of stay in the maternity ward. In 2010, the average length of stay in the maternity ward after normal delivery in Slovenia was 4.0 days while in Sweden, UK and USA it was substantially shorter, 2.3, 1.8 and 2.1 days, respectively (19). With longer postnatal hospital stay, the chance that a clinical deterioration due to duct closure occurs before discharge is higher.

Even if the current pre-discharge detection rate of critical CHD in Slovenia seems satisfactory, one out of ten newborns with such a condition still leaves the maternity ward undetected. The proportion of undetected babies may increase in the future, if the trend towards earlier discharge continues. The vast majority of undetected patients in our series, 14 out of 15, had left heart obstructive lesions, most of them coarcta-

tion of the aorta. This is not surprising, as coarctation of the aorta may develop and progress in days after birth and is not always duct-dependent. Critical left heart obstructive lesions are occasionally difficult to detect timely even in neonates additionally screened by pulse oximetry (11,12). Nevertheless, we believe that implementation of a nation-wide neonatal pulse oximetry screening as an adjunct to the prenatal cardiac ultrasound and the clinical examination of the newborn would further increase the pre-discharge detection rate of major CHD. It is important to emphasize that pulse oximetry screening cannot replace a thorough physical examination that includes assessing for signs of heart failure and comparative pulse palpation.

Pulse oximetry is a well-established, inexpensive, non-invasive and accurate diagnostic test to objectively quantify oxygen saturation and thereby identify the clinically undetectable hypoxemia that might occur in newborns with critical CHD (20,21). It has been assessed as an accurate screening method for critical CHD in numerous studies (11,12,22-25). In 2012, the US Secretary of Health and Human Services recommended to add it to the uniform neonatal screening panel, which was also endorsed by the American Academy of Pediatrics (26). A meta-analysis of 13 screening studies, including almost 230,000 infants, reported a sensitivity of 76.5 %, specificity of 99.9 % and a false positive rate of 0.14 % with no difference in accuracy reported when pre-ductal and post-ductal measurements were performed versus only post-ductal measurements (14,27). It has been demonstrated that referral of all cases with positive pulse oximetry for echocardiography does not increase substantially the burden for paediatric cardiologists as only 2.3 echocardiograms with normal cardiac findings were needed for every true positive case of duct-dependent circulation (11). In addition, more than 50 % of babies with "false positive" screening for critical CHD had some other relevant pathology, most commonly unrecognised pulmonary pathology or sepsis (28,29). Pulse oximetry screening should therefore be seen as a test of neonatal well-being rather than just a test to detect critical CHD.

During the study period, screening strategies to detect CHD in Slovenia based predominantly on prenatal ultrasound and physical examination of the newborns. A short survey among neonatologists from all Slovenian maternity units revealed that since completion of the study, pulse oximetry had been gradually implemented as an additional method for detection of CHD in all Slovenian maternity units. However, different maternity units use different protocols and no data exist whether the results of institutional screening had elsewhere been validated.

In conclusion, current pre-discharge detection rate of critical CHD in Slovenia is satisfactory. However, one tenth of the affected babies still leave the maternity ward undetected. The proportion of undetected babies may increase in the future if the trend towards earlier discharge is to be continued. The high pre-discharge detection rate could be further improved by a nation-wide neonatal pulse oximetry screening programme. In addition to critical CHD, pulse oximetry screening could detect other potentially dangerous neonatal conditions.

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6. Ethical approval

The study design was approved by the National Medical Ethics Committee of the Republic of Slovenia (no.35/10/14).

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