Gaps in Clinical Studies in Patients with Critical Congenital Heart Disease

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Abstract: The purpose of this study was to assess the potential clinical examination in the early diagnosis of patients with CCHD.

Patients and Methods: Retrospectively were followed 272 newborns and infants up to 3 months of age with CCHD for 25 years (1987-2011) from the region of North-East Bulgaria. The cardiac malformations were divided into 3 groups: obstructive lesions of the systemic circulation (OLSC) – 103 children, obstructive lesions of the pulmonary circulation (OLPC) – 64 children and non-obstructive mixing cardiopathies (NMCP) – 105 children. It were analyzed the initial clinical symptoms, place and manner of the disease detection, the discharged neonates without established heart disease and those with placed wrong or incomplete primary diagnosis.

Results: The incidence of the CCHD was 12.5% of CHD. The mean time of the initial clinical manifestation was 3.45 days, which is shorter in newborns with OLPC – 1.8 days, and the longest is in OLSC – 4.5 days ($p<0.05$). In 44.4% initial clinical symptoms were established during the first day, and by day 4 – in 81.7%. Most often the first clinical symptom is cyanosis – 65%. In 21% of cases there was no significant murmur. The average age of diagnosis is 8.5 days and was significantly lower in OLPC – 4.2 days, compared to OLSC – 9.5 days and NMCP – 10 days ($p<0.05$). By day 4 were diagnosed 54% of CCHD and 27.7% of the infants with manifested initial symptoms (81.7%) remained without diagnosis. Usually the initial diagnosis is put in the children's hospitals – 60% and only 30% in the neonatology units. Without established heart disease are discharged 15.8% of newborns, primarily with coarctation of the aorta, total anomalous pulmonary venous return and transposition of the great arteries. Initial diagnosis was incorrect in 22%.

Conclusion: The physical examination in newborn CCHD is unsatisfactory and the diagnosis is often delayed, especially in the cases of OLSC and same of NMCP. That is why screening programs are needed for early detection of these patients to improve their prognosis.

Keywords: Critical congenital heart disease, life-threatening cardiovascular malformations, neonates, clinical presentation, diagnosis.

The critical congenital heart diseases (CCHD) are group of diseases, which appear immediately after birth with life-threatening symptoms – heart failure, cardiogenic shock and or severe hypoxemia. They need urgent operation or transcatheter intervention or finishes with death usually during the first month of life. The early diagnosis in those newborns is absolutely important for the prognosis and the outcome of the treatment [1-5].

The aim of this study was to assess the potential clinical examination in the early diagnosis of patients with CCHD.

PATIENTS AND METHODS

272 newborns and infants, up to 3 months of age, with CCHD from the region of North-East Bulgaria were retrospectively followed for a period of 25 years (1987-2011). The children from male sex prevail – 162 (60%) *vs.* 110 (40%) from female sex. The average following time was 6.2 years and the maximum 25 years. The urban population prevails – 71% (193) of the children. Depending on the heart malformation the patients were divided into 3 groups – obstructive lesions of the systemic circulation (OLSC) -103 (37.9%) children, obstructive lesions of the pulmonary circulation (OLPC) – 64 (23, 5%) children and non-obstructive mixing cardiopathies (NMCP) – 105 (38.6%) children. In 98 (36%) of the patients was found one ventricle heart anatomy and in 82 (30%) there was accompanying extracardiac malformations and syndromes. Premature and immature were 61 (22.4%) of the newborn. Family burden with CHD was found in 24 (8.8 %) children.

Retrospectively were analyzed the initial and the leading symptoms, the time, the place and the way of putting the diagnosis, the newborns discharged from the neonatology units (NU) without cardiac disease and those with incorrect initial diagnosis. Methods of investigation include: clinical examination, electrocardiography, conventional radiography, echocardiography and cardiac catheterization. In some of the cases surgical and autopsy protocols were used.

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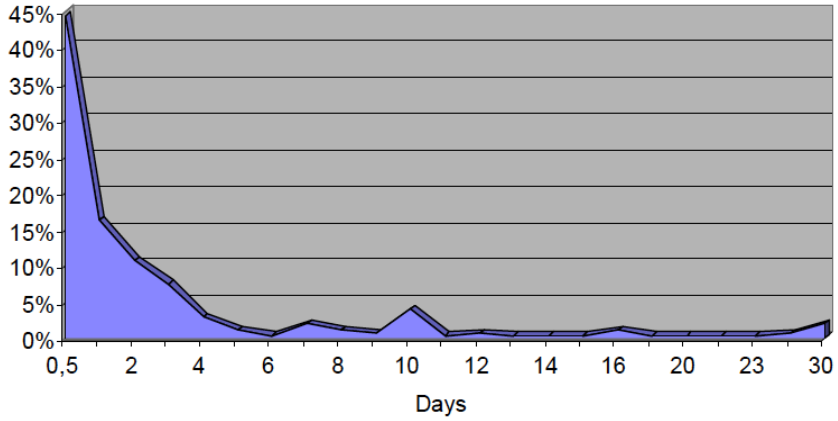

Figure 1: Time of the initial clinical manifestation in infants with CCHD.

RESULTS

The frequency of CCHD in the North- East Bulgaria is 12.5% from the whole group of CHD (n=2171) or 22 % of the diagnosed in the neonatal period (n=1232). The most frequent are: transposition of the great arteries (TGA) – 23%, critical coarctation of the aorta (CoA) – 16% and hypoplastic left heart syndrome (HLHS) – 10%, totally ½ (49%) of all the critical cardiopathies.

In 44.4% early clinical symptoms pointing CHD were found on the first day after birth, in 61% during the first two days and in 81.7 % - up to the fourth day after birth (Figure **1**).

The mean time of initial clinical appearance is 3.45 days (95% CI: 2.7 – 4.2). The shortest time is in patients with OLPC – 1.8 days (95% CI: 1.0 -2.6) followed by those with NMCP – 3.3 days (95% CI: 1.9 - 4.8) and OLSC – 4.5 days (95% CI: 3.3 -5.8). By help of one factor dispersion analyzing (ANOVA), it was established that there is a significant difference between the groups ($p<0.05$). The Duncan's post hoc multiple comparisons test showed that the difference is significant between the newborns with OLPC and OLSC. Up to the 15th day, initial manifestations were found in 100% of the patients with OLPC (Figure **2**).

The earliest initial clinical appearance is presented in newborns with pulmonary atresia with intact septum (PA/IS) – an average of 1.2 days, TGA and tricuspid atresia (TA) – 1.6 days, HLHS -1.7 days, and the latest is in CoA – 7.3 days and total anomalous pulmonary venous return (TAPVR) – 10.4 days.

The most frequent initial symptom in patients with CCHD is cyanosis - 65%, alone or in combination with heart murmur - 50% with/or appearance of cardiac failure (CF) - 31%. Cyanosis, as an initial symptom, was significantly most often seen than CF ($p<0.05$). In about 1/5 of the cases (21%) there was no significant

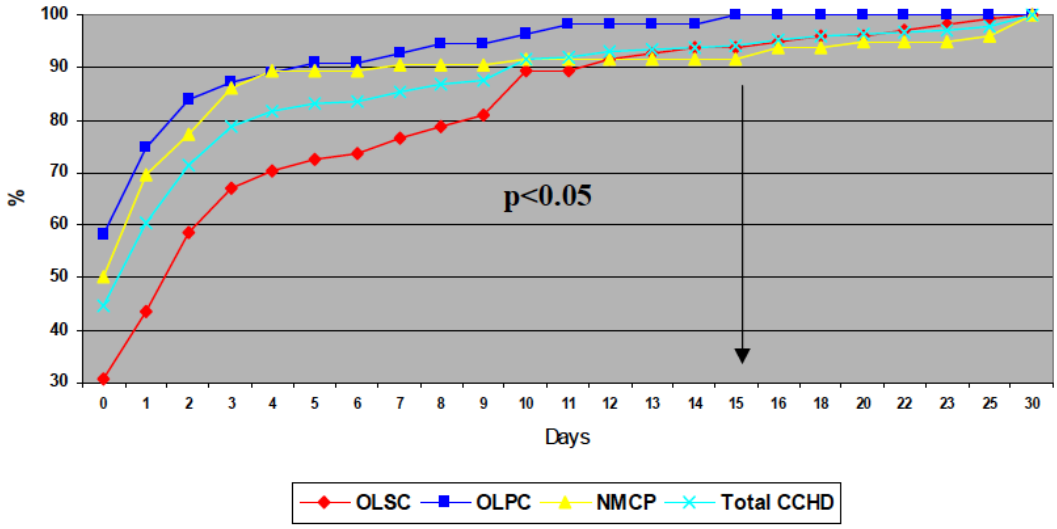

Figure 2: Initial clinical manifestation of the different groups CCHD.

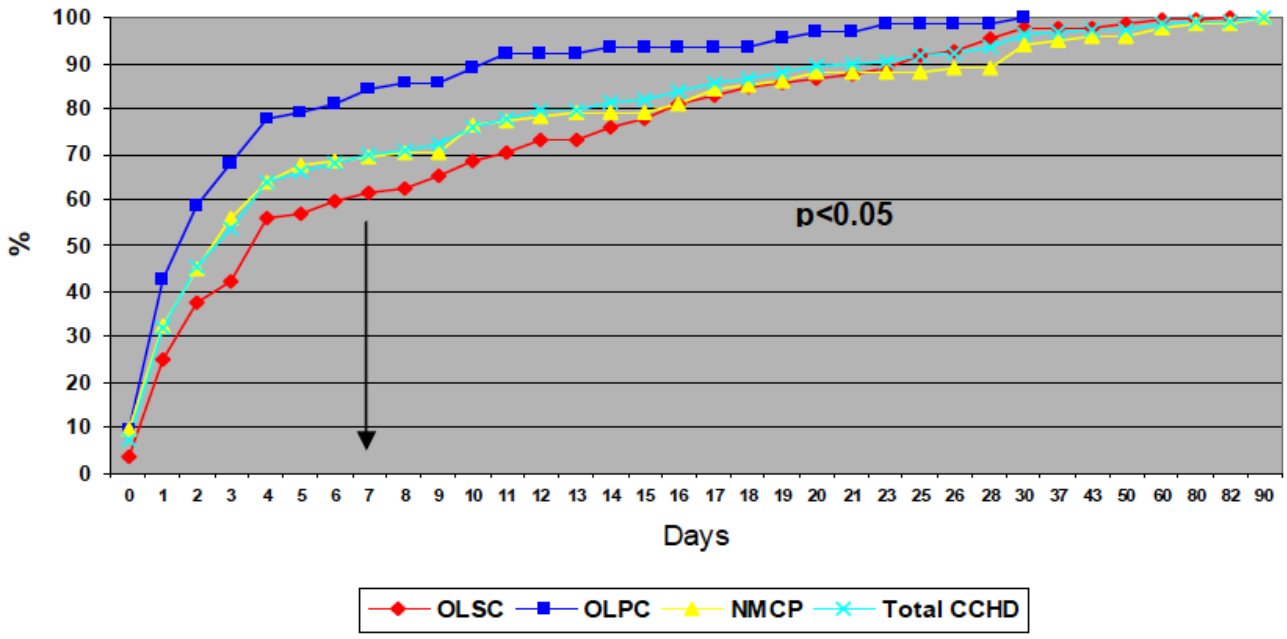

Figure 3: The time of diagnosis of the various groups CCHD.

heart murmur, usually in the newborns with PA/IS - 40%, common ventricle (CV) and malformations in visceral heterotaxy syndrome - 38%, and TAPVR - 33%.

The age of the initial diagnosis in our patients with CCHD is an average of 8.5 days (95 % CI: 6.8 – 10.2). For OLPC it is 4.2 days (95% CI: 2.8 - 5.7), for OLSC – 9.5 days (95% CI: 7 -12), and for NMCP - 10 days (95% CI: 6.7-13.4). By a one–way ANOVA ($p<0.05$) and non-parametrical test of Kruskal-Wallis ($p<0.005$) was found a significant difference between the groups. A post hoc test of Duncan showed a significant difference in the time of the initial diagnosis for the patients with OLPC and those with OLSC and NMCP. Till the end of the first week the diagnosis was made in 84.1 % of patients with OLPC, 69.6 % - for NMCP and 61.6 % - for OLSC. Initial diagnosis set after the 1-st month, we have found in 10 (3.7%) children, mainly with NMCP and OLSC: TGA, TAPVR, CoA and CV (Figure **3**).

When comparing the time of detection and the initial clinical manifestation, it was found that till the 4th day 81.7 % of the newborns with CCHD had initial clinical symptoms, with a set diagnosis in 54% - i.e. over ¼ (27.7%) of the cases remain undiagnosed (Figure **4**).

The mean delay time from the appearance of the initial clinical symptoms to the diagnosis is 5 days:

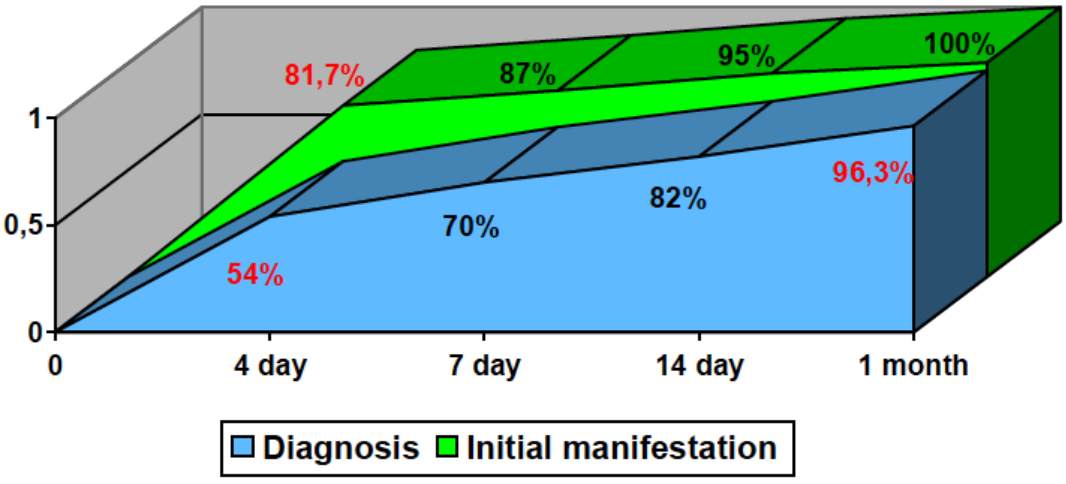

Figure 4: Time for initial manifestation and detection in patients with CCHD.

OLPC – 2.1 days, OLSC – 5.4 days, and for NMCP – 6.1 days. It took longest time for TAPVR – 10.1 days, TGA – 8.8 days, CoA and other complex cardiopathies – 6.8 days.

The place of setting the initial diagnosis, according to the medical documentation, was specified for 269 children with CCHD. In Neonatal Units (NU) of north–east Bulgaria were diagnosed 81 (30%) newborns, in pediatric units – 162 (60%) patients, fetal - 2 and in outpatient clinic – 3 children (1.1%). The diagnosis was autopsied in 21 (7.8%) patients (Figure **5**). There is no statistical dependency in the place of setting the diagnosis for the different groups CCHD – OLSC, OLPC and NMCP ($p > 0.05$).

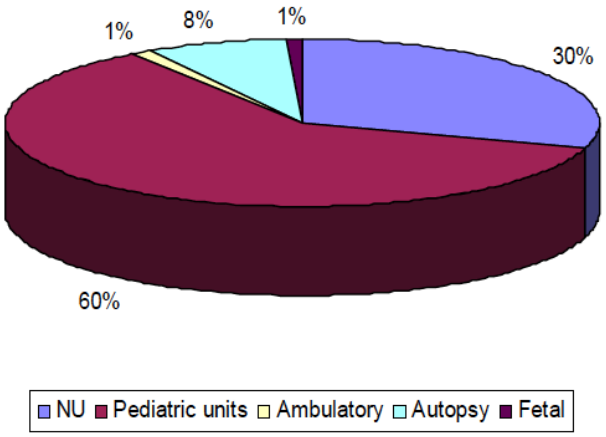

Figure 5: Place for setting of initial cardiologic diagnosis.

Without detected cardiac pathology at NU are discharged 43 (15.8%) of the newborns with CCHD. One-third of the cases in the group refer to CoA - 33%, TGA - 14% and TAPVR - 12%, in total - 59% (Figure **6**). From all the cases with TAPVR 38.5 % were discharged undiagnosed, CoA – in 32.6% and TGA – in 9.4% of the cases.

In the process of analysis of the discharged newborns without being diagnosed, according to the group of CCHD, a significantly low frequency was proved in patients with OLPC - only 3 (4.8%) infants, (standardized residual of -2.2). The differences with other groups is significant ($p<0.05$) i.e. omit predominantly patients with OLSC and NMCP (Figure **7**).

It was found that over the years the number of patients, who leave the NU without being diagnosed with cardiac malformation, is not decreasing. For the period of 1987-1999 there were 17 (15.45%) cases and for the period 2000-2010 - 26 (16.05%). The average duration of hospitalization was 6.6 days and it is not shortening in the recent years - 6.9 days *vs.* 5.5 days for the first period of the study (Table **1**).

Incorrect or incomplete initial diagnosis was set in 60(22%) of our patients with CCHD, which hides a risk, by the means of incorrect management. In the group, again the most frequent are cases with: CoA/IAA – 21.7%, TGA – 20% (mainly complex), and TAPVR – 10% (total 51.7%). The diagnosis was incorrect in 46.2% of all the patients with TAPVR and 27.1 % in those with CoA/IAA (Table **2**).

The time, required for correction of the diagnosis, was average 11.8 days. The total time of 23.4 days for setting the correct diagnosis is significantly longer compared to the mean time , needed for all the patients with CCHD - 8.5 days ($p<0.001$).

It was found that the relative part of the wrong and incomplete initial diagnoses is decreasing during the recent years, without significant differences. For the period of 1987 to 1999 there were 26.4% and for the period 2000-2011 – 19.1% (Table **3**).

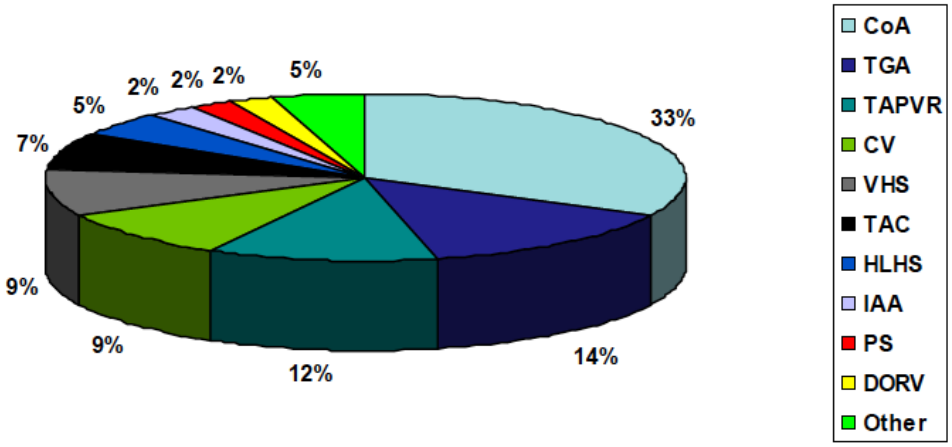

Figure 6: Newborn with CCHD discharged from NU without cardiac diagnosis.

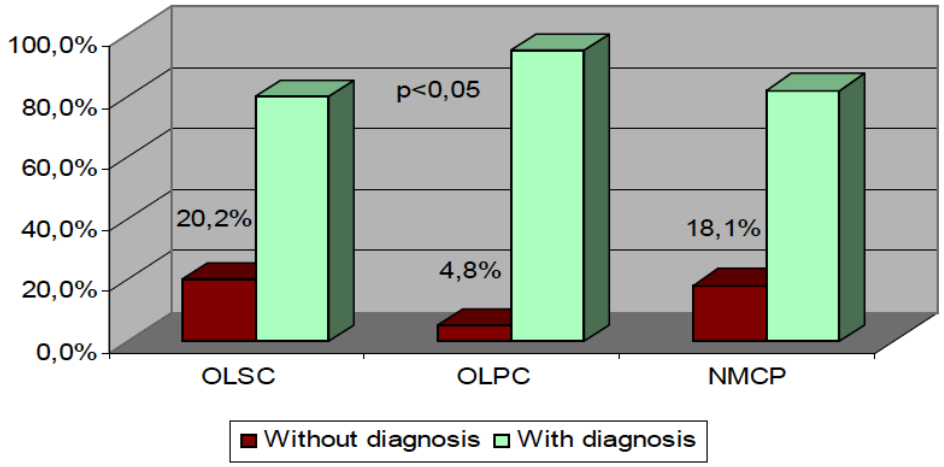

Figure 7: Discharged newborns without detected cardiac pathology.

Table 1: Infants with CCHD Discharged from NU without Cardiac Diagnosis Over the Years

Years	CCHD	Discharged without diagnosis		Average hospitalization (days)
		Count	Percentage	
1987-1999	110	17	15,45%	5,5
2000-2011	162	26	16,05%	6,9
Total	**272**	**43**	**15,80%**	**6,6**

Table 2: CCHD with Wrong or Incomplete Primary Diagnosis

CCHD	Incorrect diagnosis		Total count CCHD	Percentage of specific CCHD
	Count	Percentage		
CoA/IAA	13	21,70%	48	27,10%
TGA	12	20%	64	18,80%
TAPVR	6	10%	13	46,20%
CV	4	6,70%	17	23,50%
HLHS	4	6,70%	27	14,80%
PA/VSD	3	5%	15	20%
TAC	3	5%	19	15,80%
VHS	3	5%	22	13,60%
TA	2	3,30%	12	16,70%
PS	1	1,70%	7	14,30%
Other	1	1,70%	4	25%
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Total	**60**	**100%**	**272**	**22%**

Table 3: Patients with Incorrect Primary Diagnosis Over the Years

Years	CCHD	Incorrect initial diagnosis		
		Count	Percentage	Significance
1987-1999	110	29	26,4%	p>0,05
2000-2011	162	31	19,1%	
Total	**272**	**60**	**22 %**	

DISCUSSION

The frequency of the CCHD in the region of north-east Bulgaria, we have established in our research, is 12.5% of all the CHD and 22% of those with neonatal manifestation and it does not differ significantly from the data, presented in the literature – from 15% [1, 6] to 25% of all the CHD [7-9]. The differences in the frequencies can be explained with the framework of the examined group of patients and the specific methods of investigations.

The Northeastern part of Bulgaria is a large region without pediatric cathlab and pediatric cardiac surgery unit. When diagnosed, the patients must be referred to the National Heart Hospital, the only place in Bulgaria, where the complete care can be performed.

We have established that in a significant part of the newborns with CCHD the first clinical signs of cardiac pathology can be detected in the first few days of life in the neonatology units (NU): 44.4% during the first day of life, 61% during the first two days of life and 81.7% till the fourth day of life. The mean time of initial clinical presentation for the whole group is 3.45 days, and for the OLPC it is the shortest time of presentation – 1.8 days. The latest clinical manifestation have OLSC - on the average 4.5 days, which is shared by other authors as well [10-12]. That is why it is indispensable a specific clinical examination of the newborns about these cardiac malformations. Das and colleagues (2012) recommend investigation of the b-type natriuretic peptide for early identification and treatment of newborns with OLSC [13].

The cyanosis, as an early symptom, has a very high frequency (65%) and that is in the maintenance of the initiation of the pulse oximetry screening (POS) as a standard routine procedure in the NU. Several of the latest publications demonstrate the advantages of this screening as high specific, moderately sensitive and meets the criteria for universal screening [14-22].

During our research we discovered that heart murmur, as an early symptom, is examined in a half of the newborns with CCHD at the debut of the cardiac disorder. Clarke and Kumar (2005) consider that newborns with noticeable heart murmur, who are discharged from NU need to be followed up during the next 4-6 weeks and it is advisable that parents are acquainted with the symptoms of the significant CHD [23]. According to different authors in 54% to 86% of the newborns with noticeable heart murmur, a CHD is diagnosed using echocardiography [24, 25]. A heart murmur in the neonatal period is established in 57% of the infants, who passed out from CHD after discharged from NU [26] and in 38% of the patients with obstructive lesions of the left heart, who developed congestive heart failure until the 6 week of life [11].

In 21% of the observed patients with CCHD in our research, there was a lack of a significant heart murmur even in a clinically manifested cardiac disease, which, as other authors emphasized, does not exclude the availability of cardiac malformation [24, 27].

The mean time of which our patients with CCHD were diagnosed is 8.5 days and it took far more time for NMCP and OLSC in comparison to OLPC. More than one-fourth of the newborns with CCHD and initial clinical presentation during the first four days of life remained undiagnosed. It is noted an average time delay of around 5 days in the initial clinical manifestation and it is more significant in patients with TAPVR, TGA and CoA. Our results are similar to the results, published by other authors, according to which the diagnosis is most often delayed in newborns with OLSC [11, 12] or in cases with CoA, IAA and TAPVR [6]. A special observation is required for newborns and infants discharged from NU for such kind of cardiac malformations.

Most often our patients with CCHD have been diagnosed in the pediatric hospitals (60%) and only 30% in the NU. Kovacikova and colleagues (2007) report that in 34% of the patients with obstructive lesions of the left heart the diagnosis was made in a transitional medical institution [28]. According to the literature data during the past few years, the part of the diagnosed cases in the NU is increasing. In a research, conducted by Wren and colleagues (1999) out of 1067 infants with CHD, 82% of them were discharged from NU undiagnosed and 35% of them were having clinical symptoms or died before the age of 6 weeks [29]. Wren and colleagues (2008) report that the main part of the patients with CCHD are found in NU – 62%, after discharge – 25%, through fetal echocardiography – 8% and post-mortem – 5% [6]. The percentage of post-mortem diagnose in our patients with CCHD is not higher, than those presented in the literature data [10, 12, 30].

Approximately 16% of the newborns with CCHD in our research were discharged from NU without being diagnosed with a cardiac malformation and their percentage is not decreasing during the recent years.

Patients with OLSC are most often undiagnosed, as well as NMCP, but infants with OLPC are rarely missed – only in 4.8%. Unidentified remain 38.5% of the children with TAPVR and 32.6% with CoA. According to the literature database the relative percentage of the undiagnosed in the NU newborns with CCHD is between 12% and 50% [32], and most closely to our results are the findings, published by Meberg and colleagues (2008) – 12% [31] and Mellander and colleagues (2006) – 20% [33]. In a research, conducted by Mellander and colleagues, it is announced that out of 259 children, who had undergone interventional procedures until the age of two months, 20% of the newborns with CCHD were discharged undiagnosed from NU. Significantly more often the diagnosis is being late in infants with ductal-dependant systemic circulation (30%) and duct-independent cardiophaties-38% in comparison to ductal-dependant pulmonary circulation – only in 4% (p<0,001). Authors determine a substantial increasing during the years (1993-2001) of the portion of the newborns discharged undiagnosed – from 13% to 26% (p<0.05) [33]. According to Wren and colleagues (2008), every third child, who has life-threatening CHD is discharged undiagnosed, and most often that happens in cases with CoA-54%, IAA – 44%, and TAPVR – 37% [6]. Aamir and colleagues (2007) also report that the diagnosis is most often delayed in children with CoA and the time, when the final diagnosis is made, is between 3 days and 6.5 months [32]. In a publication from 2013 Mouledoux and Walsh announced that before the introduction of POS, 75% of the undiagnosed cases with CCHD, turned out to be CoA and it seems that this is the most often missed cardiac malformation, even after the initiation of the screening [34]. According to Dawson AL and colleagues (2013) 22.9% of the children were discharged undiagnosed and the level of the NU is an independent factor [35]. In USA approximately 4800 children with CCHD are born every year and 280 of them are discharged form NU without being diagnosed and about 10% of the duct-dependent CHD remain undiagnosed until death [30].

According to our results in more than one-fifth of the cases with CCHD (22%) the initial cardiology diagnosis was inaccurate – false or incomplete. The time, needed for correction of the diagnosis was roughly 11.8 days. Inadequate initial diagnosis was made in 46.2% of all the cases with TAPVR and in 27.1% in those with CoA/IAA. Research, conducted by Ainsworth and colleagues (1999) report twice as much mistaken initial diagnosis – 44%, mostly in complex cardiophaties, obstructive lesions of the left heart and TAPVR [24].

CONCLUSION

The clinical examination in patients with CCHD is with unsatisfactory sensitivity. More than one-fourth of the newborns with clinically manifested symptoms till the fourth day after birth remain undiagnosed. Newborns are discharged from NU without being diagnosed in 15.8% and in 22% the initial diagnosis is incorrect or incomplete. Most often are missed children with OLSC and some NMCP – CoA, IAA and TAPVR. The initiation of screening programs in the NU for early identification of patients with CCHD is necessary and that will help for improvement of their prognosis.

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