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The effect of prenatal diagnosis on antibiotic therapy in neonates with hypoplastic left heart syndrome. Antibiotics in prenatally diagnosed patients with HLHS

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Abstract: Introduction: Hypoplastic left heart syndrome (HLHS) is a congenital heart anomaly that is diagnosed prenatally or postnatally. The prenatal diagnosis leads to limiting the rate of systemic complications in the preoperative period due to optimization of the early therapeutic management.
Objective: The objective of the study is to determine the effect of prenatal diagnostic management of HLHS on the condition of newborns and the frequency of antibiotherapy employment prior to the first stage of surgical treatment.
Methodology: The study included 95 children with HLHS operated on in the years 2014–2016. The cohort was divided into two groups: newborns with a prenatally diagnosed heart defect (50 children — 52.6%) and neonates with the defect diagnosed after birth (45 children — 47.4%). The data of the patients were analyzed based on their medical records.
Results: The mean age of the children upon admission was 3.86 days in the group of patients with the prenatally diagnosed heart defect (PreHLHS) and 7.41 days in the group of newborns without the prenatal diagnosis (PostHLHS) ($p = 0.001$). In 60% of the PreHLHS group patients (30/50), at least one antibiotic was administered, while in the PostHLHS group, antibiotherapy was employed in 93.3% (42/45) cases ($p = 0.001$). Bacteriological tests demonstrated pathogen growth in 33 children (36% and 33.3%, respectively), what accounted for 34.7% of the entire cohort. On the average, the first antibiotic was introduced on the 6.55th day of life in the PreHLHS group and on the 2.73th day in the PostHLHS group ($p = 0.005$). The most profound differences in antibiotic employment involved aminoglycosides. The aforementioned type of antibiotic medications was administered to 6% of the children with the prenatal diagnosis and to 17.8% of the children diagnosed postnatally ($p = 0.042$).

C o n c l u s i o n s: Preoperative antibiotherapy in children with HLHS was employed more frequently than it would be indicated by microbiology tests results.
Antibiotics were observed to be introduced more commonly and earlier in the newborns with the postnatally diagnosed congenital heart defect.

Key words: prenatal diagnosis, hypoplastic left heart syndrome, antibiotherapy, Norwood operation.

Introduction

Hypoplastic left heart syndrome (HLHS) is the most common complex single ventricle-type congenital heart defect [1]. The syndrome may include hypoplastic or absent left ventricle, mitral valve stenosis or atresia, aortic valve stenosis or atresia and ascending aorta and aortic arch hypoplasia [2]. To date, the etiology of the defect is unknown.

At present, thanks to the development of diagnostic techniques, the diagnosis of HLHS may be established as early as in the first trimester of fetal life [3]. Prenatal echocardiography allows for detecting approximately 90% of cases of left heart hypoplasia [4]. Diagnosing the defect is an indication for surgical treatment; the method of choice is a multi-stage surgical procedure, with the Norwood procedure as the initial palliation [5, 6]. The clinical picture of HLHS develops over the first several days of life in consequence of the ductus arteriosus closure. The resultant symptoms of cardiogenic shock resemble the symptoms of septic shock and this is why the patient is erroneously diagnosed as a victim of an intrauterine infection. The effect is administration of antibiotics. The prenatal diagnosis of the defect allows for an early intravenous infusion of prostaglandin E1, thus contributing to decreasing the morbidity rate acting through the mechanism of increasing cardiovascular capacity, improving organ perfusion, renal function and decreasing the incidence of neurological complications [7]. The prenatal diagnosis does not affect survival rates after the first stage of treatment; early prevention of the neonate developing circulatory insufficiency protects the newborn from acidosis and multi-organ failure that is manifested by increased concentration levels of lactates, creatinine and alanine aminotransferase [8–11]. In case a congenital infection is suspected, broad-spectrum chemotherapeutic agents are recommended. Nevertheless, they have nephrotoxic (aminoglycosides, cephalosporins), ototoxic and even cardiotoxic (aminoglycosides) effects [12, 13]. The prenatal diagnostic management provides an opportunity to protect the general condition of the newborn and to promptly transport the child to a cardiac surgery center, but it also may affect preventing the development of adverse effects of the administered antibiotics [14].

Material and Methods

The investigation was carried out based on the retrospective analysis of medical records of 95 neonates with HLHS operated on in the years 2014–2016. Depending on the time when the defect was diagnosed, the cohort was subdivided into two groups: newborns with prenatally diagnosed PreHLHS (n = 50) and newborns without prenatally diagnosed PostHLHS (n = 45). The statistical analysis included demographic data, age and inflammatory state parameters upon admission to the cardiac surgery center, age at the time of the Norwood procedure, identified bacterial pathogens, anatomical HLHS variants and 30-day postoperative mortality rates. Additionally, the authors analyzed the association between the time and type of the employed antibiotherapy and the results of bacteriology.

The statistical analysis employed the chi-square test, univariate U Mann-Whitney and t-Student tests for independent variables and was carried out using the Statistica 10 software (Statsoft), with the significance level assumed to be $p < 0.05$.

The objective of the study was the analysis of the effect of the prenatal diagnostic management of hypoplastic left heart syndrome on the preoperative use of antibiotics prior to the Norwood procedure.

Results

The mean age of the newborns upon admission to the cardiac surgery center was 3.86 days in the PreHLHS group and 7.41 days in the PostHLHS group ($p = 0.001$). The minimal age at the onset of hospitalization in both groups was the day of birth, while the maximal age was different for the two groups, amounting to 11 days in the PreHLHS group and to 25 days and in the PostHLHS group.

The age of the majority of the neonates from the two groups ranged between the 1st and 20th day of life. The children with prenatally diagnosed heart defects were operated on the 15th day of life on the average, while the remaining newborns between the 16th–18th day of life ($p = 0.489$). One-half of the PreHLHS neonates were subjected to a cardiac surgical procedure between the 1st and 10th day of life. In the group of patients without the prenatal diagnostic management, the procedure was most commonly performed between the 11th and 20th day of life; such timing was seen in 66.7% of the subjects. The chance that it would be possible to perform the procedure in the group with the prenatal diagnosis between the 1st and 10th day after birth was almost twofold higher as compared to the group without the prenatal diagnosis (OR = 2.04).

The mean preoperative hospitalization time was 10.75 days for all the newborns. The preoperative hospitalization time of the PreHLHS neonates (11.85) did not significantly differ from the time noted in the PostHLHS group (9.77) ($p = 0.193$) (Table 1).

Table 1. Preoperative hospitalization of neonates with HLHS. The results are presented in the averaged form. Statistical significance p <0.05.

	Newborns with prenatally diagnosed HLHS	Newborns without prenatal diagnosis of HLHS	Total	p
Birth body mass (g)	3217.9 (± 510.9)	3296.1 (± 630.5)	3253.5 (± 566.1)	0.544
Age upon admission to cardiosurgical center (days)	3.86 (± 2.56)	7.41 (± 5.77)	5.73 (± 4.85)	0.001
Age upon the Norwood procedure (days)	15 (± 9.57)	16.18 (± 6.26)	15.57 (± 8.14)	0.489
Time of preoperative hospitalization in cardiosurgical center (days)	11.85 (± 8.54)	9.77 (± 5.18)	10.75 (± 6.99)	0.193

Mechanical ventilation was required by seven children from the PreHLHS group (14%) and 13 children (29%) from the PostHLHS group.

Of the inflammatory state parameters (C-reactive protein, aspartate aminotransferase, alanine aminotransferase, creatinine, WBC and blood platelet count) assessed upon admission to the ward, the activity of liver enzymes significantly differentiated between the groups (p = 0.035 and 0.007). The mean activity of alanine and aspartate aminotransferases approximated the upper normal limit (39.85 IU/l and 49.54 IU/l, respectively) in the group with the prenatally diagnosed defects. In the remaining children, the mean ALT and AST values were 55.14 IU/l and 69.35 IU/l (Table 2).

Table 2. Biochemical parameters in preoperative blood tests. The results are presented in the averaged form. Statistical significance p <0.05.

Inflammatory state parameter	Newborns with prenatally diagnosed HLHS	Newborns without prenatal diagnosis of HLHS	Reference values for newborns	p value
C-reactive protein (mg/l)	6.73 (± 4.05)	6.55 (± 3.62)	<10	0.838
Aspartate aminotransferase (IU/l)	49.54 (± 21.46)	69.35 (± 58.39)	<40	0.035
Alanine aminotransferase (IU/l)	39.85 (± 20.12)	55.14 (± 29.27)	<40	0.007
Creatinine (µmol/l)	68.93 (± 24.68)	83.46 (± 51.18)	28–78	0.097
White blood cells (thousands/µl)	13 742.86 (± 4 321.41)	15 211.91 (± 6 647.18)	4.0–10.8 × 103	0.209
Blood platelets (thousands/µl)	334.10 (± 135.61)	304.98 (± 173.82)	150–450	0.372

All the admitted patients had echocardiography performed in order to determine the precise anatomy of the defect prior to the first stage of surgical treatment of HLHS.

Bacteriological tests were performed in materials originating from blood, urine, stool and throat smears (Table 3). The results were available within up to 24 hours. Pathogen growth was demonstrated in 33 children (PreHLHS — 36%; PostHLHS — 33.3%), what accounted for 34.7% of the entire cohort (p = 0.33). In the PreHLHS group, the most common pathogen was Staphylococcus epidermidis (50% positive results), while in the PostHLHS group — Escherichia coli (86.7%) (Table 4). Both in the group of neonates in whom the culture showed pathogen growth and in the newborns where no such growth was noted, the first antibiotic agent was introduced in the 4th–5th day of life (p = 0.291).

Table 3. Bacteriological results in materials collected from blood, stool, urine and throat smears.

BLOOD CULTURE		
	With prenatal diagnosis	Without prenatal diagnosis
Performed in:	11 children (22%)	7 children (16%)
Positive in:	7 children	3 children
Pathogens detected:	13 (7 species)	3 (3 species)
	Staphylococcus epidermidis — 6 Escherichia coli — 2 Staphylococcus haemolyticus — 1 Streptococcus viridians — 1 MRCNS — 1 Acinetobacter spp. — 1 Enterococcus spp. — 1	Staphylococcus epidermidis — 1 Escherichia coli — 1 Streptococcus parasanguinis — 1
STOOL CULTURE		
	With prenatal diagnosis	Without prenatal diagnosis
Performed in:	7 children (14%)	9 children (20%)
Positive in:	6 children	9 children
Pathogens detected:	6 (3 species)	18 (8 species)
	Escherichia coli — 2 Klebsiella pneumoniae — 2 Pseudomonas aeruginosa — 1	Escherichia coli — 8 Klebsiella pneumoniae — 2 Pseudomonas aeruginosa — 2 Enterococcus faecalis — 2 Enterococcus faecium — 1 Staphylococcus haemolyticus — 1 Staphylococcus epidermidis — 1 Citrobacter freundii — 1

Table 3. Cont.

URINE CULTURE		
	With prenatal diagnosis	Without prenatal diagnosis
Performed in:	5 children (10%)	4 children (9%)
Positive in:	3 children	3 children
Pathogens detected:	3 (3 species)	4 (3 species)
	Enterococcus faecalis — 1 Staphylococcus epidermidis — 1 Streptococcus spp. — 1	Enterococcus faecalis — 1 Escherichia coli — 2 Enterococcus faecium — 1
THROAT SMEAR		
	With prenatal diagnosis	Without prenatal diagnosis
Performed in:	5 children (10%)	4 children (9%)
Positive in:	5 children	3 children
Pathogens detected:	8 (5 species)	9 (6 species)
	Streptococcus viridians — 3 Staphylococcus epidermidis — 2 Pseudomonas aeruginosa — 1 Escherichia coli — 1 Klebsiella pneumoniae — 1	Streptococcus viridians — 3 Escherichia coli — 2 Pseudomonas aeruginosa — 1 Staphylococcus epidermidis — 1 Klebsiella pneumoniae — 1 Haemophilus influenza — 1

Table 4. Pathogens detected in microbiological tests*, including single methicillin-resistant coagulase-negative Staphylococci (MRCNS) strains.

Pathogen	Newborns with prenatally diagnosed HLHS	Newborns without prenatal diagnosis of HLHS	Total
Gram-negative bacteria	**14**	**25**	**39**
Escherichia Coli	5	13	18
Klebsiella pneumoniae	4	3	7
Enterococcus spp.	2	4	6
Pseudomonas aeruginosa	2	3	5
Haemophilus spp.	0	1	1
Acinetobacter spp.	1	0	1
Citrobacter spp.	0	1	1
Gram-positive bacteria	**16**	**8**	**24**
Staphylococcus epidermidis	9	3	12
Staphylococcus haemolyticus	1	1	2
Streptococcus spp.	6*	4	10

In the PreHLHS group, antibiotherapy was employed in 60%, while in the PostHLHS group — in 93.3% of the children (p = 0.001). The first antibiotic was administered at the mean age of 6.55 days of life in the PreHLHS group and on the 2.73th day in the PostHLHS group (p = 0.005).

In the PreHLHS patients, several antibiotics were more commonly employed, while in the PostHLHS group, mono-antibiotherapy predominated (especially penicillin derived antibiotics). The most pronounced intergroup differences in antibiotic usage were observed in the case of aminoglycosides (p = 0.042) (Table 5). Antibiotics employed in the course of surgery to prevent infections were excluded from the analysis.

Table 5. Antibiotics employed preoperatively depending on bacteriology culture results. Statistical significance p <0.05.

Type of antibiotic	Newborns with prenatally diagnosed HLHS		Newborns without prenatal diagnosis of HLHS		p value
	Negative culture	Positive culture	Negative culture	Positive culture	
Penicillins	0	8	6	11	0.065
Cephalosporins	6	5	9	2	0.760
Aminoglycosides	0	3	3	5	0.042
Glycopeptide antibiotics	2	6	1	4	0.391
Carbapenems	1	3	4	3	0.198
Others	0	2	5	1	0.128
Total	**9**	**27**	**28**	**26**	

In both groups of newborns in whom antibiotherapy was employed in spite of negative bacteriological results, cephalosporins were statistically more commonly used as compared to the remaining kinds of antibiotics (p = 0.022). On the other hand, in the newborns whose bacteriology results were positive, penicillin derived antibiotics were statistically more commonly administered (p = 0.002), as well as glycopeptide antibiotics (p = 0.040).

The mean time of hospitalization in the Cardiosurgical Intensive Care Unit following the Norwood procedure was 40.6 days in the PreHLHS group and 48.58 days in the PostHLHS group.

Discussion

Development of diagnostic methods has resulted in the fact that serious heart defects, such as HLHS, may be detected as early as during the first cardiological examination

of the fetus that is performed between the 14th and 15th weeks of gestation [15]. In the years 2008–2012 in Europe, the percentage of HLHS cases detected prenatally was 73.8% [16]. In Poland, the data are similar [17]. Detection of a congenital heart defect in the intrauterine period is associated with significant clinical consequences. A neonate with prenatally diagnosed hypoplastic left heart syndrome may reach a cardiac surgery center in the 1st or 2nd day of life in good general condition. This allows for standardization and optimization of perioperative management. The time in which the prenatally diagnosed newborns were transported to the authors' center was almost twofold shorter as compared to the children who were diagnosed after birth (4 days vs. 7 days).

A neonate with HLHS that is not subjected to treatment in the first days of life begins developing cardiogenic shock. In the face of symptoms suggestive of an infection, broad-spectrum antibiotic therapy is empirically introduced, yet, it does not result in any improvement [18]. Such a management mode should be regarded justified in view of the highly common occurrence of congenital infections in neonates. In the present study, the authors demonstrated a significant difference in antibiotics employment between the two groups. Antibiotic use predominated among the children who were diagnosed after birth (60% vs. 93%). The tendency was even more apparent when the time of the first antibiotic introduction was analyzed. In the group of the neonates with a prenatally diagnosed heart defect, the first antibiotic was administered on the average on the 6th day after admission, while the remaining children received the medication on the 2nd day of hospitalization. The percentage of the children who were administered chemotherapeutics was more than twofold higher than the percentage of the neonates in whom bacteriology demonstrated pathogen growth. The analysis of the two groups demonstrated that the ratio was 1.67 in the neonates diagnosed prenatally and 2.8 in the group with the postnatal diagnosis. It does not necessarily mean that in some cases, the medications were groundlessly administered, since the sensitivity of a bacterial culture ranges between 50% and 80%, depending on the collected material.

As it follows from the study, the differences in antibiotic administration were mainly seen in case of aminoglycosides. Their use was almost threefold lower among the children diagnosed before birth. All aminoglycosides exert a stronger or weaker ototoxic and nephrotoxic effect [19]. Inasmuch as renal dysfunctions are regarded to be reversible [20], hearing impairment is a permanent complication of aminoglycoside therapy [21]. Audiometry demonstrated that the problem of ototoxicity may involve as many as 62.3% of all patients treated with the aforementioned medications [22]. Factors that increase the risk of toxicity include among others age — newborns, low initial creatinine clearance, lung and liver diseases. Neonates with diagnosed heart defects were observed to be administered antibiotics more frequently and earlier.

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