

Clinical Study

Umbilical Neutrophil Gelatinase-Associated Lipocalin Level as an Early Predictor of Acute Kidney Injury in Neonates with Hypoplastic Left Heart Syndrome

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Acute kidney injury (AKI) is a primarily described complication after unbalanced systemic perfusion in neonates with congenital heart defects, including hypoplastic left heart syndrome (HLHS). The aim of the study was to compare the umbilical NGAL concentrations between neonates born with HLHS and healthy infants, as well as to analyze whether the determination of NGAL level could predict AKI in neonates with prenatally diagnosed HLHS. Twenty-one neonates with prenatally diagnosed HLHS were enrolled as study group and 30 healthy neonates served as controls. Perinatal characteristics and postnatal parameters were extracted from the hospital neonatal database. In umbilical cord blood, we determined plasma NGAL concentrations, acid base balance, and lactate and creatinine levels. In neonates with HLHS, complications (respiratory insufficiency, circulatory failure, NEC, IVH, and AKI) were recorded until the day of cardiocurgery. We observed in neonates with HLHS higher umbilical NGAL levels compared to controls. Among 8 neonates with HLHS and diagnosed AKI stage 1, we observed elevated NGAL levels in comparison to those newborns without AKI. Umbilical NGAL could predict, with high sensitivity and specificity, AKI development in study neonates. We suggest that the umbilical blood NGAL concentration may be an early marker to predict AKI in neonates with HLHS.

1. Introduction

Hypoplastic left heart syndrome (HLHS) accounts for 1–4% of all congenital heart defects (CHD) [1, 2]. Nevertheless, it is the most common cause of death resulting from cardiac anomalies in the first month of life [2, 3]. Recent approaches focused on understanding and decreasing the frequency of morbidity and complications, including acute kidney injury (AKI) in children with CHD [4]. AKI is an independent predictor of mortality in critically ill neonates and children [5, 6]. The currently available data suggest a trend towards reduced mortality and better renal recovery with earlier initiation of prevention procedures such as monitoring and fluid balance in the subclinical stage of kidney injury [7, 8].

The definition of AKI in a neonate has changed in recent years, and detection is now mostly based on monitoring serum creatinine levels, with or without urine output [9].

Serum creatinine-based definitions fail to delineate the severity, timing, and cause of renal injury. Furthermore, in the first days of neonatal life, creatinine concentrations reflect maternal values (placental transfer) and that serum creatinine level in neonates depends on gestational and postnatal age [9–14].

The quest to find early markers of AKI in neonates is of vital importance [15].

In particular, NGAL is emerging as an excellent biomarker in urine and plasma, for the early prediction of AKI, for monitoring clinical trials in AKI, and for

the prognosis of AKI in several common clinical scenarios [16, 17]. The most promising marker of renal injury/damage is neutrophil gelatinase-associated lipocalin (NGAL), secreted by renal tubular epithelium and excreted in the urine during normal renal function [18–20]. NGAL is a protein that is highly upregulated in the proximal tubules after ischemic AKI [21]. Plasma NGAL levels rise markedly after epithelial damage following ischemic/reperfusion kidney injury in neonates after an episode of perinatal asphyxia [22, 23]. NGAL has also been initially introduced in patients with CHD undergoing cardiosurgery [16, 24].

Aim of the Study. The aim of the study was to compare the umbilical plasma NGAL concentrations between neonates born with HLHS and healthy infants, as well as to analyze whether the determination of umbilical NGAL level could be used as an early marker of kidney injury in neonates with prenatally diagnosed HLHS.

2. Materials and Methods

Our prospective clinical study was performed from January 2013 to January 2014 in the Department of Neonatology, Medical University of Silesia in Katowice, Poland. The study attained an approval from the Human Ethics Committee of the Medical University of Silesia. Before birth, written parental consent was obtained. Patient care and monitoring were performed as part of the hospital's standard protocol, and no specific intervention, other than the collection of umbilical cord blood, was required for this research.

Preterm neonates (below the 37th week of gestation), children with other congenital abnormalities or chromosomal anomalies, newborns of mothers suffering from diabetes mellitus, hypertension, preeclampsia, and children of multiple pregnancies and metabolic disorders were excluded from the study. We also excluded neonates with evidence of congenital infections, as well as those that were born to mothers with clinical chorioamnionitis.

In the preoperative period, we assessed the incidence of respiratory insufficiency, if the neonate required oxygen therapy administration through a nasal cannula, nasal continuous positive airway pressure or mechanical ventilation, circulatory insufficiency when the neonate required inotropic support, necrotizing enterocolitis (NEC), intraventricular haemorrhage (IVH), and acute kidney injury (AKI) [25, 26]. AKI was defined, in accordance with the Acute Kidney Injury Network (AKIN) criteria, as persistently increased serum creatinine (>1.5 mg/dL) for at least 24 hours or rising values > 0.3 mg/dL from the baseline [9, 27].

2.1. Study Group Examination. Among 1,271 neonates born in our unit, we enrolled 21 neonates with prenatally diagnosed HLHS, as the study group. In order to assess the comparison of NGAL levels in plasma of umbilical cord blood, 30 healthy, full-term newborns, residing in the unit during the study, were enrolled as the control group.

We evaluated the correlation between the incidence of complications in the early preoperative period and umbilical

NGAL levels in neonates with HLHS. Characteristics of the study and control groups are presented in Table 1.

Among 21 infants diagnosed with HLHS, all children from the first day of life presented signs of circulatory failure, 80% had signs of respiratory insufficiency requiring ventilatory support, 38% of children developed AKI stage 1, 9.5% of neonates had NEC, and 14.3% had IVH.

A similar frequency of preoperative complications such as respiratory insufficiency (62% versus 46%; $P = 0.18$) and circulatory failure (100% versus 80%; $P = 0.22$), NEC (12% versus 15%; $P = 0.61$), and IVH (24% versus 23%; $P = 0.57$) was observed in HLHS neonates presenting AKI as compared with HLHS neonates without AKI. Neither of the neonates with HLHS required preoperative renal replacement therapy. There were no differences in mortality (38% versus 46%; $P = 0.09$) and length of stay in our unit (12 versus 14 days; $P = 0.73$) before cardiac surgery, between HLHS neonates with AKI and without AKI (Table 2).

2.2. Laboratory Performances. During childbirth, 5 milliliters of blood was collected from the umbilical artery from the placental side, as a standard protocol of our hospital. Blood morphology with total counts of white blood cells (WBC) and neutrophils (manual method) as well as acid-base balance, lactate, creatinine, and NGAL concentrations were performed in all investigated neonates. Umbilical cord blood samples were centrifuged at 2500 revolutions/minute for 10 minutes, and plasma was then stored until assayed at -70°C , in accordance with the recommendations by BioVendor. Plasma NGAL concentrations were determined using the sandwich enzyme immunoassay for the quantitative measurement of human lipocalin-2 (BioVendor—Laboratorní medicína a.s., Brno, Czech Republic). The detection limit of the assay was 0.02 ng/mL.

2.3. Statistical Analysis. Continuous variables were compared using Mann-Whitney or Kruskal-Wallis tests, while categorical variables were compared using Chi-square or Fisher's exact tests. The differences and correlations between different analyzed parameters were performed using Kruskal-Wallis test and Spearman's rank test.

Quantitative variables were presented as median and 95% confidence intervals, whereas qualitative variables were shown as percentages. The validity of umbilical NGAL level as a diagnostic marker was assessed using sensitivity and specificity. Statistical analysis was performed using standard procedures available in STATISTICA 10 (Statsoft Polska Inc.) and MedCalc Software Version 12.7.4. Statistical inferences were based on the level of significance $P < 0.05$.

3. Results

We observed significantly higher concentrations of NGAL in umbilical cord blood of children with HLHS compared with controls (91.1 ng/mL, 95% CI: 35.9–152.4 ng/mL versus 31.0 ng/mL, 95% CI: 22.9–36.4 ng/mL; $P < 0.001$). No significant difference was found in the creatinine level of neonates from the study and control groups (0.8 mg/dL, 95%

TABLE 1: Baseline characteristics according to study and control groups (Kruskal-Wallis test, Chi-square test)*.

Study group	Neonates HLHS-AKI (n = 8)	Neonates HLHS no-AKI (n = 13)	Controls (n = 30)
Gestational age (weeks)	37 [37, 39]	38 [37, 39]	39 [37, 40]
Gender: female (%)	3 (35%)	5 (40%)	12 (40%)
Apgar score in 5th min (pts)	8 [7, 9]	7 [7, 8]	9 [8, 9]
Delivery			
Vaginal delivery (%)	0	4 (30%)	10 (35%)
Cesarean section (%)	8 (100%)	9 (70%)	20 (65%)
Blood gas analysis			
pH			
>7.2	5 (62%)	7 (54%)	14 (47%)
<7.2	3 (48%)	6 (46%)	16 (53%)
HCO ₃ (mmol/L)	19.8 [16.1, 21.8]	21.4 [20.5, 23.1]	23.6 [22.4, 24.3]
BE (mmol/L)	-6.8 [-13.4, -3.4]	-5.9 [-7.4, -4.6]	-2.4 [-3.6, -1.6]
Lactate (ng/mL)	6.3 [3.2, 9.2]	3.5 [2.5, 4.0]	1.9 [1.7, 2.2]
Creatinine (mg/dL)	0.9 [0.8, 1.1]	0.8 [0.7, 0.8]	0.7 [0.6, 0.9]
White blood cell count [×10 ⁹ /L]	15.4 [14.0, 22.2]	14.8 [9.8, 23.2]	15.2 [5.6, 20.5]
Total neutrophil count [×10 ⁹ /L]	10.1 [5.1, 14.1]	8.9 [5.9, 13.4]	5.1 [2.6, 10.5]

*Results shown as medians and [95% confidence intervals] or percentages.

TABLE 2: Differences between mortality, length of stay, and frequency of complications occurring in the group of neonates with HLHS and AKI in comparison with the group of children with HLHS no-AKI (Mann-Whitney U test, Chi-square test)*.

Study group	Neonates HLHS-AKI (n = 8)	Neonates HLHS no-AKI (n = 13)	P value
SaO ₂ before surgery (%)	89 [88–93]	91 [88–95]	0.73
Length of stay in NICU	12 [11–16]	14 [12–18]	0.32
Mortality before procedure (%)	3 (38%)	6 (46%)	0.09
Respiratory failure (%)	5 (62%)	6 (46%)	0.18
Circulatory insufficiency (%)	8 (100%)	10 (80%)	0.22
Necrotising enterocolitis (%)	1 (12%)	1 (8%)	0.57
IVH II (%)	1 (12%)	1 (8%)	0.57
IVH III-IV (%)	1 (12%)	2 (15%)	0.61

*Results shown as medians and [95% confidence intervals] or percentages.

CI: 0.7–1.0 mg/dL versus 0.7 mg/dL, 95% CI: 0.6–0.9 mg/dL; P = 0.06). However, a higher total count of neutrophils

was detected in the umbilical blood (10.1 versus 5.1 × 10⁹/L; P = 0.04), without any significant difference in the total WBC count (15.4 versus 15.2 × 10⁹/L; P = 0.51) in newborns with HLHS as compared with the control group.

Furthermore, umbilical NGAL concentrations in neonates with HLHS and diagnosed AKI were significantly higher in comparison to other newborns with HLHS without AKI (171 ng/dL, 95% CI: 66.1–187 ng/dL versus 29 ng/dL, 95% CI: 23–42 ng/dL; P < 0.001)—Figure 1. ROC curve analysis demonstrated a critical level of NGAL in the umbilical cord blood > 66.6 ng/mL, and this allows with 80% sensitivity (95% CI: 28–99%) and 89.5% specificity (95% CI: 72–99%) predicting AKI in newborns with HLHS (Figure 2). We also found a significant correlation between umbilical plasma NGAL level and severity of acidosis (lactate (r = 0.29; P = 0.005) and HCO₃ concentrations (r = -0.25; P = 0.02)) in newborns with HLHS. However, there was no correlation between umbilical plasma NGAL and umbilical creatinine concentrations in neonates with HLHS (r = -0.11; P = 0.23). We also found a correlation between NGAL levels and total neutrophil count in neonates with HLHS (r = 0.32; P = 0.04) (Table 3). We did not observe any difference in preoperative oxygen saturation between neonates with HLHS and AKI and those without AKI (89%, 95% CI: 79–92% versus 91%, 95% CI: 82–95%; P = 0.51). There were no correlations between NGAL level in umbilical cord blood and neonatal mortality (r = 0.24; P = 0.54) and preoperative complications (NEC

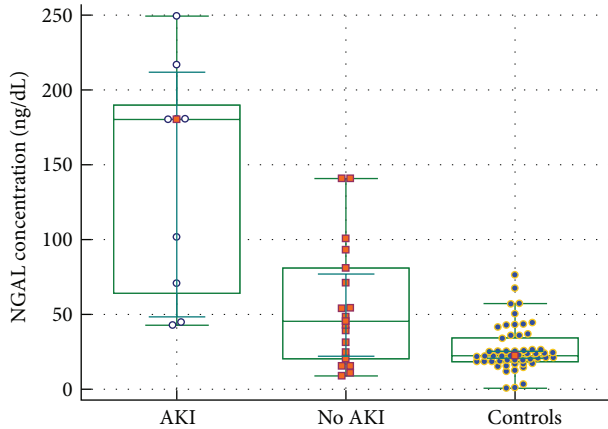


FIGURE 1: Umbilical NGAL values in three investigated groups of neonates (HLHS-AKI, HLHS-no AKI, and controls). Medians and 95% confidence intervals: maximum and minimum are shown.

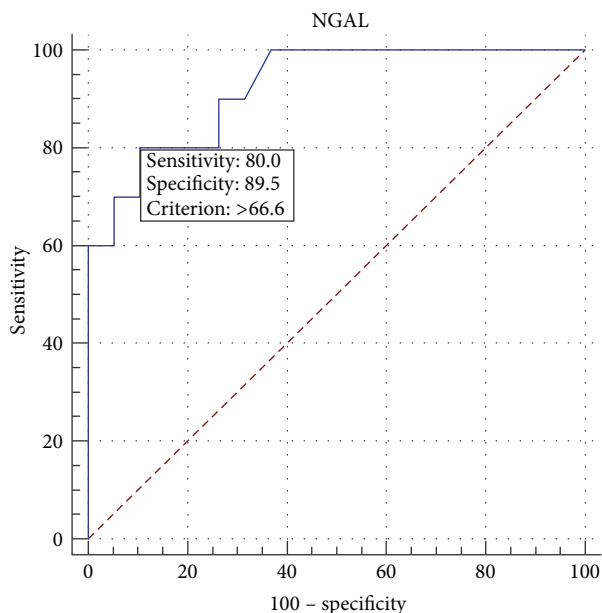


FIGURE 2: Receiver-operating-characteristic curve is shown for NGAL cord blood concentrations in relation to AKI. Cut-off value for umbilical NGAL 66 ng/dL resulting in a sensitivity of 80% and a specificity of 89.5%. * Area under ROC curve, AUC = 0.92 (95% CI: 0.76–0.98; $P < 0.0001$); likelihood ratios, +LR = 7.6 (95% CI: 2.0–29.2); –LR = 0.22 (95% CI: 0.06–0.8).

($r = 0.14$; $P = 0.67$), respiratory insufficiency ($r = 0.53$; $P = 0.36$), circulatory insufficiency ($r = 0.74$; $P = 0.07$), or IVH ($r = 0.67$; $P = 0.37$) in neonates with HLHS.

4. Discussion

To the best of our knowledge, NGAL has never been investigated in umbilical cord blood in neonates with prenatally diagnosed HLHS complicated by AKI.

The present study focused on determining whether plasma NGAL concentrations in neonates born with HLHS,

measured in umbilical arterial blood, could play an important role in AKI prediction. Literature regarding this topic reveals that acute or chronic dysfunction of the heart or kidneys results from a failure of one of the organs, which then may lead to damage of another organ. This dysfunction is known as cardiorenal syndrome (CRS) [28, 29]. In our opinion, in the case of some children with HLHS, CRS may complicate the course of the disease.

This can be confirmed by elevated levels of umbilical NGAL level in neonates with HLHS compared to the control group and significantly higher levels of plasma NGAL in neonates who developed AKI in the first day of life, despite normal serum creatinine levels. ROC analysis showed high sensitivity and specificity for early diagnosis of kidney injury, by determining the umbilical plasma NGAL concentration in newborns with HLHS.

We believed that AKI in neonates with HLHS could complicate the preoperative period; however, it occurred that complications such as respiratory failure and circulatory insufficiency, NEC and IVH, length of stay in hospital, and mortality were similar in HLHS newborns with and without AKI. Our results opposed those of Theilen and Shekerdeman [30]. These authors suggested that complications such as mesenteric ischemia leading to severe NEC, and hypoxic-ischemic kidney injury or haemorrhagic cerebral damage, can ultimately preclude cardiocirculatory intervention.

Absence of a viable left ventricle leads to dilatation and hypertrophy of the right ventricle. The right ventricle experiences an increase in volume load, as blood is diverted away from the underdeveloped left side. Both the systemic and pulmonary vasculatures are perfused via the right ventricle and pulmonary artery, with patency of the ductus arteriosus assuring blood supply to the systemic circulation [31]. The decrement in cardiac output and disturbance in systemic circulation may explain the limitations in somatic growth seen in these fetuses and impaired neurodevelopmental outcome [32–34].

In our opinion, the disturbance in systemic circulation occurring in foetuses with HLHS can also lead to kidney injury. Kidneys normally receive up to 5% of the cardiac output during the fetal period and seem to be very sensitive to hypoperfusion and ischemic insults [35, 36]. Decreased renal blood flow may also be attributable to high renal vascular resistance from an imbalance between renal vasoconstriction and vasodilation, and this may lead to kidney injury, and metabolic acidosis additionally accelerates this process [22, 23, 37, 38]. We have shown that NGAL concentration correlates with the severity of metabolic acidosis (concentration of lactate, HCO_3 , and base deficit) in neonates with HLHS.

Furthermore, we observed that NGAL level correlated with a higher total number of neutrophils in the umbilical blood of neonates with HLHS and AKI, because the increased neutrophil count had been the result of perinatal asphyxia. Morkos et al. showed similar results [39–41].

As a consequence of the relatively small sample size, the statistical power of this comparison between AKI and no-AKI patients is limited. In addition, an absence of consensus over the definition of AKI in neonates complicates comparability between studies.

TABLE 3: Correlations between selected parameters measured in umbilical cord blood in investigated newborns with HLHS and umbilical NGAL levels (Spearman's rank correlation).

	Creatinine [mg/dL]	Lactate (ng/mL)	HCO ₃ (mmol/L)	Base deficit (mmol/L)	Total neutrophil count (×10 ⁹ /L)
NGAL level [ng/mL]					
Correlation coefficient	0.17	0.29	-0.25	-0.42	0.32
Significance level <i>P</i>	0.2	0.005	0.02	<0.001	0.04

In conclusion, an increase, especially in cord blood NGAL levels, in neonates with HLHS may be indicative of tubular injury, as a result of CRS, without changes in serum creatinine. This so-called subclinical kidney injury is very difficult to detect. Introduction of appropriate nephro-protective treatment at this stage can prevent the newborn from developing renal insufficiency in the future. It is known that approximately 50% of pediatric patients, who presented AKI in their medical history, showed signs of chronic renal insufficiency [12].

Furthermore, to the best of our knowledge, our study is novel, demonstrating the association between the amount of congenital heart defects with cardiorenal signaling and biomarker of kidney injury. Therefore, confirmation by future prospective multicentre cohorts is needed to assess NGAL concentration, at which one would expect the occurrence of AKI in the first days of life, in order to implement the appropriate treatment as soon as possible.

Conflict of Interests

The authors declare that there is no conflict of interests regarding the publication of this paper.

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