Umbilical cord blood NGAL concentration as an early marker of perinatal asphyxia in neonates

Stężenie NGAL w krwi pępowinowej jako wczesny marker niedotlenienia okołoporodowego u noworodków

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Abstract

Introduction: Recent reports have revealed increased concentration of neutrophil gelatinase-associated lipocalin (NGAL) in cardiovascular diseases and after episodes of hypoxia. We hypothesized that elevated plasma NGAL levels could be a result of vascular endothelial injury due to perinatal asphyxia.

Materials and methods: Ninety-three newborns with a gestational age ≥37 weeks, of which 32 newborns were asphyxiated (study group), and 61 were healthy children (control group), were enrolled in the study. Serum NGAL, lactate and creatinine concentrations, acid-base balance, neutrophil and white blood cell count were measured in the umbilical cord blood.

Results: Asphyxiated newborns had a significantly lower pH value (7.0 vs. 7.3; p<0.001), lower HCO3 (15.8mmol/L vs. 23.2mmol/L; p<0.001) and higher lactate concentrations (7.5mmol/L vs. 2.3mmol/L; p<0.001), as compared to controls. Neutrophil count (10.3x10⁹/L vs. 6.5x10⁹/L; p=0.02) and NGAL concentration (122.5ng/mL vs. 24.3ng/mL p<0.001) were elevated in asphyxiated newborns as compared to healthy children.

Conclusions: The measurement of NGAL in the umbilical blood can be a valuable biomarker of perinatal asphyxia in neonates.

Key words: newborn / asphyxia / NGAL /

Słowa kluczowe: noworodek / niedotlenienie / NGAL /

Streszczenie

Wstęp: Badania z ostatnich lat wykazały wzrost stężenia lipokainy związanej z żelatynazą neutrofili (NGAL) w chorobach sercowo-naczyniowych i po epizodach niedotlenienia. Chcielibyśmy sprawdzić, czy zwiększone stężenie NGAL w surowicy może być wynikiem uszkodzenia śródbłonia naczyń w wyniku niedotlenienia okołoporodowego.

Materiał i metoda: Do badań zakwalifikowano 93 noworodki w wieku płodowym >37 tygodni ciąży, w tym 32 z objawami niedotlenienia i 61 zdrowych dzieci jako grupa kontrolna. W surowicy krwi pępowinowej oznaczano stężenia NGAL, laktatów, kreatyniny, równowagę kwasowo-zasadową oraz liczbę neutrofili i krvinek białych.

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Wyniki: Noworodki z objawami niedotlenienia miały znacznie niższą wartość pH (7,0 vs 7,3; p<0,001), niższe stężenie HCO3 (15,8mmol/L vs 23,2mmol/L; p<0,001) i większe stężenie mleczanów (7,5mmol/L vs 2,3mmol/L; p<0,001) w porównaniu z grupą kontrolną. Liczba neutrofili (10,3x109/L vs 6,5x109/L; p=0,02) i stężenie NGAL (122,5ng/mL vs 24,9ng/mL; p<0,001) było znacząco wyższe u noworodków z grupy niedotlenionych w porównaniu z grupą kontrolną.

Wnioski: Oznaczanie NGAL z krwi pępowinowej może być ważnym markerem w diagnostyce niedotlenienia okołoporodowego.

Słowa kluczowe: noworodek / niedotlenienie / NGAL /
Table I. Characteristics of newborns enrolled in the study.

<table>
<thead>
<tr>
<th>Variable</th>
<th>Asphyxiated group n=32</th>
<th>Control group n=61</th>
<th>p*</th>
</tr>
</thead>
<tbody>
<tr>
<td>Me (min./max.)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>WG [wk]</td>
<td>37.9 (37.0; 40.0)</td>
<td>38.2 (37.0; 41.0)</td>
<td>NS</td>
</tr>
<tr>
<td>Birthweight [g]</td>
<td>2914 (2055; 4300)</td>
<td>3141 (2250; 4440)</td>
<td>NS</td>
</tr>
<tr>
<td>Apgar 5th min. [pts]</td>
<td>5 (0; 7)</td>
<td>8 (6; 10)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Gender f/m [%]</td>
<td>50/50</td>
<td>48/52</td>
<td>NS</td>
</tr>
<tr>
<td>Hb [g/dL]</td>
<td>16.1 (13.6; 18.3)</td>
<td>15.1 (9.2; 19.2)</td>
<td>NS</td>
</tr>
<tr>
<td>Neutrophils [10^9/L]</td>
<td>10.3 (1.1; 19.4)</td>
<td>6.5 (2.9; 12.5)</td>
<td>0.02</td>
</tr>
<tr>
<td>WBC [10^9/L]</td>
<td>17.7 (5.4; 18.5)</td>
<td>15.4 (6.5; 17.3)</td>
<td>NS</td>
</tr>
<tr>
<td>HCO3 [mmol/L]</td>
<td>15.8 (8.0; 23.8)</td>
<td>23.3 (17.9; 29.7)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Lactate [mmol/L]</td>
<td>7.5 (2.6; 17.7)</td>
<td>2.3 (1.0; 6.5)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>pH</td>
<td>7.0 (6.8; 7.2)</td>
<td>7.3 (7.2; 7.4)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Serum creatinine [mg/dL]</td>
<td>0.9 (0.4; 1.5)</td>
<td>0.7 (0.4; 1.2)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Serum NGAL [ng/mL]</td>
<td>122.5 (38.5; 273.0)</td>
<td>24.3 (3.3; 88.3)</td>
<td>&lt;0.001</td>
</tr>
</tbody>
</table>

Me – Median; WG – weeks of gestation; Hb – hemoglobin; WBC – white blood cells; NGAL – neutrophil gelatinase-associated lipocalin.; p* – from Mann-Whitney U test

Table II. NGAL concentration in the study and the control groups.

<table>
<thead>
<tr>
<th>pH</th>
<th>N</th>
<th>Me (min./max.)</th>
<th>p*</th>
</tr>
</thead>
<tbody>
<tr>
<td>(1) pH &lt; 7.0</td>
<td>23</td>
<td>154.5 (60.5; 273.0)</td>
<td></td>
</tr>
<tr>
<td>(2) pH 7.1-7.2</td>
<td>13</td>
<td>89.4 (38.5; 180.6)</td>
<td></td>
</tr>
<tr>
<td>(3) pH &gt;7.2</td>
<td>57</td>
<td>31.5 (11.7; 130.0)</td>
<td></td>
</tr>
</tbody>
</table>

Me – Median; NGAL – neutrophil gelatinase-associated lipocalin.; p* <0.05 – ANOVA (Kruskal-Wallis test)

(15.8mmol/L vs. 23.2mmol/L; p<0.001), and higher lactate concentrations (7.5mmol/L vs. 2.3mmol/L; p<0.001) in the study group as compared to the control group. Neutrophil count was significantly elevated in asphyxiated children in comparison to healthy controls (10.3x10^9/L vs. 6.5x10^9/L; p=0.02). There were no observable differences in the hemoglobin level (16.1g/dL vs. 15.1g/dL; p>0.05), and white blood cell (WBC) count (17.7x10^9/L vs. 15.4x10^9/L), between newborns from the study group and controls.

We noted an elevated NGAL concentration (122.5ng/mL vs. 24.3ng/mL; p<0.001) and creatinine level (0.9mg/dL vs. 0.7mg/dL; p<0.001) in the asphyxiated group as compared to the control group. Furthermore, we also observed increased NGAL and serum creatinine levels (>1.5 mg/dL) in 6 newborns suffering from AKI from the study group in comparison to asphyxiated non-AKI infants (122.5ng/mL vs. 176.3ng/mL; p=0.05) and controls (176.3ng/mL vs. 24.3ng/mL; p<0.001) – Figure 1.

We noticed an inverse correlation between the concentration of NGAL and the general well-being of neonates assessed according to the Apgar score at 5 minutes (r=-0.37; p<0.05), and pH value of the umbilical blood (r=-0.55; p<0.05) (Table II), while a positive correlation between NGAL and lactate concentrations of the umbilical blood (r=0.57; p<0.05), as well as the neutrophil count therein (r=0.15; p<0.05), was found.

Figure 1. Umbilical cord serum NGAL concentration in asphyxiated AKI and non-AKI neonates, and controls.
Discussion

We compared the serum level of NGAL in neonates with symptoms of acute perinatal asphyxia to healthy controls. According to our results, asphyxiated neonates, especially those that suffered from AKI, had significantly increased levels of NGAL, in comparison to those that were non-asphyxiated. Similar results had been attained by Raggal NM et al., and Sarafidis et al., [6, 8].

Additionally, we established that the concentration of NGAL correlated with low Apgar score at 5 minutes, and increasing metabolic acidosis, suggesting that NGAL could possibly be a valuable indicator of perinatal asphyxia.

Neutrophil gelatinase-associated lipocalin, known as the innate immunity antibacterial factor, is released in insignificant amounts by activated neutrophils in several human tissues. This factor is grossly induced as a response to a variety of injuries to epithelial and renal tubular cells [10, 11, 12].

Asphyxia, including perinatal asphyxia, is known to cause damage to the walls of blood vessels. This has been proven in studies by several authors, for example Nako et al., and Buchner et al., [3, 14]. Vascular wall damage provides a significant source of NGAL in serum through the activation of neutrophils. Some authors suggest its role in the inflammatory reaction, following an incidence of asphyxia and vascular wall remodeling due to injury, as the reason for enhanced NGAL expression from activated neutrophils [6, 15].

In our study, we also observed an increased value of neutrophils in asphyxiated infants, especially those who developed AKI, in comparison with the control group, and the asphyxiated group without AKI. Perhaps the damage to the vascular wall and developing inflammatory process therein activated neutrophils, which are the source of NGAL. This can be confirmed by the positive correlation obtained between the number of neutrophils and NGAL concentration. Inflammation as a result of asphyxia cannot be ruled out in our study.

Endothelial injury may lead to multiorgan damage, with the most severe complications affecting the central nervous system, cardiovascular system, and kidneys [16].

Most recent studies have suggested that NGAL may be a sensitive and early biomarker of AKI, detected both in serum and urine of patients in just a few hours after the damaging factor had been activated, which is in contrast to creatinine, whose increased concentration only appears after 24-48 hours, resulting in delayed diagnosis and treatment. In case of asphyxia in neonates, determining the degree of kidney function on the base of creatinine concentration is unreliable, as serum creatinine level in newborns in the first few days of neonatal life reflects maternal renal function due to placental transfer [17, 18, 19].

A small number of asphyxiated neonates enrolled into the study group was the main limitation of our investigation.

Conclusion

In conclusion, asphyxiated neonates demonstrate significantly increased NGAL levels in comparison to healthy controls, and the measurement of this biomarker in umbilical blood following acute asphyxia can be of significant diagnostic value. Due to the positive correlation demonstrated between NGAL and the Apgar score, as well as umbilical pH value, it seems safe to assume that NGAL could serve as a valuable marker of asphyxia in neonates.

Oświadczenie autorów

1. Piotr Sumiak – autor założeń pracy, analiza statystyczna wyników, przygotowywanie manuskryptu i pisemnictwa – autor zgłaszający i odpowiedzialny za manuskrypt.

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5. Zofia Walencka – uzyskanie funduszy na realizację badań laboratoryjnych, autor koncepcji i założenia pracy, analizy i interpretacji wyników, ostateczna weryfikacja i akceptacja manuskryptu.

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References


