Károly Streitman · Anita Tóth · István Horváth · Gyula Tálosi

Renal injury in perinatal hypoxia:
ultrasonography and changes in renal function

Received: 23 March 2000 / Accepted: 14 March 2001

Abstract We studied 12 hypoxaemic neonates (5 mature newborns, birth weight 2850–4200 g, gestational age 37–41 weeks; and 7 premature newborns, birth weight 770–1850 g, gestational age 27–34 weeks;) with repeated urine and blood chemistry on the 1st and 3rd days of life. Nephrosonographical examinations on the 1st, 3rd and 5–7th days of life were also performed. As controls, 12 healthy infants were examined (gestational age 36–42 weeks; birth weight 2450–4200 g). Hypoxic neonates had higher serum creatinine and blood urea nitrogen levels. Tubular markers also demonstrated renal tubular damage. Neonates in both hypoxic groups were hyperuricaemic and hyperuricosuric, and had higher urinary protein concentrations. All these infants exhibited an increased echogenicity of the renal cortex, and 11/12 showed the same finding in the medullary area. These findings disappeared within 1 week in all infants. Among the 12 healthy control infants, no cortical hyperechogenicity was found and only three of these infants displayed transient medullary renal hyperechogenicity.

Conclusion Since the hypoxaemic infants demonstrated greatly increased urinary concentrations of uric acid and protein, we suggest that a temporary precipitation of these two agents may be responsible for the ultrasonographic findings. Circulatory redistribution might play a role in the phenomenon of cortical hyperechogenicity.

Key words Hypoxia · Neonate · Renal hyperechogenicity

Abbreviations BUN blood urea nitrogen · Cr creatinine · FE\textsubscript{Na} fractional excretion of sodium · GFR glomerular filtration rate · NAG N-acetyl-\textbeta-D-glucosaminidase · NICU neonatal intensive care unit · UA uric acid · US ultrasonography

Introduction

The overall renal function, both glomerular and tubular, is severely impaired at birth, both in absolute and in relative terms, corrected for 1.73 m\textsuperscript{2} body surface area of the adult [5]. Because of the low glomerular filtration rate (GFR), the neonatal kidneys are severely limited in their adaptive response to stress, be it disease or iatrogenic manipulations. For example the autoregulation of GFR, i.e. the maintenance of glomerular filtration when blood pressure falls precipitately, is less efficient than in the adult, which may predispose the kidneys of the newborn to hypovolaemic injury and hence oliguric or nonoliguric acute renal failure [7]. This is often seen in severe neonatal hypoxaemia or asphyxia.
The blood supply of the newborn kidneys is only 15–20% of the cardiac output, appreciably less than in the adult (around 25%). Most of the blood reaching the neonatal kidneys immediately after birth is directed to the most mature, sodium and water-conserving nephrons, located in the renal juxtamedullary region. In hours or days, the blood flow is redirected to the outer cortex, as in the adult perfusion pattern. This leaves the medullary region especially sensitive to hypoxic damage affecting a variety of local energetic processes [2].

Ultrasoundography (US) is a noninvasive, easy and relative inexpensive imaging technique, which is the examination of choice in renal diseases of the newborn. The US findings in neonates differ, however, from those in the adult. In neonates, the renal cortex is more echogenic than in adults, whereas the pyramids are relatively large and hypoechogenic. Neonatal renal hyper-echogenicity has in the past been described after hypoxic insults [3, 16]. The mechanism responsible for this phenomenon is not known. The physiological, cortical hyperechogenicity tends to persist for many months [6, 13], whereas the superimposed hyperechogenicity after hypoxic insults is far more dynamic and may change within days.

The present study was undertaken to examine the prevalence of increased renal parenchymal echogenicity secondary to neonatal hypoxic insults. The US examinations were combined with serum and urine tests, to establish whether there were correlations between the US findings and the results of the chemical tests.

### Patients and methods

#### Patients

We investigated 12 hypoxaemic neonates: 5 term newborns (gestational age 37–41 weeks, median birth weight 3250 g, range 4200–2850 g; one with a diaphragmatic hernia, four after intrapartum asphyxia, Group 1) and 7 preterm infants (gestational age 27–34 weeks, median birth weight 1440 g, range 770–1850 g; one with a diaphragmatic hernia, two with intrapartum asphyxia and four with idiopathic respiratory distress syndrome, Group 2). All patients fulfilled our criteria for hypoxaemia: Apgar score at 5 min of <4, blood pH < 7.2, PaO₂ < 40 mm Hg and blood bicarbonate level <15 mmol/l within the first 24 h of life. All patients were hospitalised in the neonatal intensive care unit (NICU) of the Department of Paediatrics, Szeged University Medical Centre. The control group consisted of 12 healthy term neonates without perinatal asphyxia, born and examined on the neonatal ward of Hódmezvásárhely Country Hospital (Group 3). The gestational age of the healthy neonates was 37–42 weeks and median birth weight 3220 g (range 2450–4200 g). All had 5 min Apgar scores > 7, an umbilical blood pH > 7.25 and PaO₂ > 40. The renal US examinations of the controls provided no evidence of any renal or urological problem.

Prior to the study, ethical approval was gained from the Committee for Ethics in Human Studies of Szeged University Medical School (51–29/1996 O.E.).

#### Methods

Soon after admission of the hypoxaemic infants to the NICU, an umbilical arterial catheter was put in place. Arterial blood samples for the electrolyte and kidney function studies were taken on the 1st post-natal day (within 8 h after the hypoxic event), while on the 3rd day of life (48–56 h), acid-base samples were taken several times, as required by the clinical course. After arrival and between the age of 48 and 56 h, 8-h urine (bag) collections were obtained. Serum creatinine (Cr), blood urea-nitrogen (BUN) and serum uric acid (UA) levels were measured, as was the urinary excretion of Cr, calcium and UA. All these examinations were performed by routine laboratory methods. The urinary activity N-acetylg glucosaminidase (NAG), a tubular lysosomal enzyme which is a sensitive marker of renal tubular injury, was assessed spectrophotometrically. The measurements were performed according to Csáthy et al. [4]. Shortly, after gel filtration of the urine on a Sephadex G-25 column, enzyme activity was measured with the substrate p-nitrophenyl-β-D-glucosaminide. The quantity of p-nitrophenyl released after the reaction was measured spectrophotometrically at 400 nm. Activities were corrected for urine Cr concentration expressed in mmol, according to the method of Jaffe, and given as μmol substrate/min per mmol creatinine. The Cr clearance was calculated via the formula UV/P, in which U and P represent the urinary and serum levels of Cr and V the volume of urine per unit time (ml/min), corrected for 1.73 m² body surface area. Additionally, the urinary UA/Cr ratio, a marker of perinatal hypoxia [1], and the fractional excretion of sodium (FeNa) were calculated. In the control group, the first blood sample was taken from the umbilical cord soon after delivery, and the 3rd day blood sample was taken by peripheral venous puncture at the age of 48–56 h. Instead of 8-h urine collections random urine samples were taken and the Cr clearance was calculated on the basis of the Schwartz formula with a k value of 0.45 [10].

Data were calculated using the two-way analysis of variance with repeated measures. In the case of unequal group variances or highly skewed distribution, ANOVA was performed after logarithmic transformation. The interaction between the two ways was examined. When the interaction was significant, the alteration between the different values of one of the factors (groups or measurement times) was checked by the other factor. In the case of non-significant interaction, differences between groups were checked independently of measurement times. Pairwise comparisons were performed by Bonferroni correction.

The US examinations were performed bedside, with a portable Hitachi EUB 450 ultrasonograph with 5 and 7.5 MHz transducers

### Table 1 Results of serum investigations in hypoxic and control (healthy) neonates.

<table>
<thead>
<tr>
<th>Group</th>
<th>Patients</th>
<th>BUN (mmol/l)</th>
<th>Cr (μmol/l)</th>
<th>UA (μmol/l)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Group 1 (n = 5)</td>
<td>7.8 (7.0–13.4)**</td>
<td>89 (78–201)**</td>
<td>582 (542–731)**</td>
</tr>
<tr>
<td>1</td>
<td>Group 2 (n = 7)</td>
<td>5.6 (3.1–7.6)*</td>
<td>65 (55–111)</td>
<td>345 (306–450)*</td>
</tr>
<tr>
<td>1</td>
<td>Group 3 (n = 12)</td>
<td>3.1 (2.3–5.9)</td>
<td>55 (44–71)</td>
<td>271 (166–391)</td>
</tr>
<tr>
<td>2</td>
<td>Group 1 (n = 5)</td>
<td>10.5 (9.0–16.5)**</td>
<td>133 (115–228)**</td>
<td>332 (256–652)*</td>
</tr>
<tr>
<td>2</td>
<td>Group 2 (n = 7)</td>
<td>7.8 (4.1–16.6)**</td>
<td>80 (51–138)</td>
<td>271 (179–401)</td>
</tr>
<tr>
<td>2</td>
<td>Group 3 (n = 12)</td>
<td>3.7 (2.5–5.9)</td>
<td>69 (41–95)</td>
<td>243 (96–355)</td>
</tr>
</tbody>
</table>

*P < 0.05 between the hypoxic groups and the control group

**P < 0.01 within groups

***P < 0.01 within groups and between hypoxic groups and control group