Bilateral adrenal bleeding: the cause of high early jaundice and acute primary adrenal insufficiency in the neonate

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Key words:
bleeding; adrenal; jaundice; acute primary insufficiency; neonate

Received: 3. 5. 2017
Accepted: 12. 10. 2017

Abstract

Adrenal bleeding in a newborn is rare. The cause of bleeding is unknown, most likely due to several factors. Bleeding may be minimal with no clinical signs or fulminant with acute adrenal insufficiency, which is a life-threatening situation that requires immediate detection and treatment.

In this paper we represent a clinical case of a term neonate born to the mother with gestational diabetes, who was hospitalised due to high early hyperbilirubinemia. Significant bleeding in both adrenal glands was identified by ultrasound and primary adrenal insufficiency diagnosed. We discuss possible causes, the diagnostic clues, the treatment of disease and its prognosis.

Cite as: Fister P, Žnidaršič Eržen M, Kotnik P, Tomažič M. [Bilateral adrenal bleeding: the cause of high early jaundice and acute primary adrenal insufficiency in the neonate]. Zdrav Vestn. 2018;87(3–4):151–8.

DOI: 10.6016/ZdravVestn.2614

1. Introduction

In the foetus, adrenal glands are vital organs and as such relatively large. Blood flow through them is bigger than in any later life period. These anatomic-physiologic factors represent a bigger risk for adrenal bleeding in the neonatal period (1). Adrenal bleeding is found present in 0.2 % of newborns, and is usually due to damage to the foetus on its passage through the birth canal during labour and delivery. The cause of the occurrence of bleeding is not known, very likely, more factors are involved. The risk factors for the occurrence of adrenal bleeding are hypoxia, asphyxia, perinatal injury, sepsis, blood clotting disorders and macrosomia (1,2). Adrenal bleeding is usually unilateral and is found present in the right adrenal gland in 70 % of cases. (3). Bilateral adrenal bleeding is rare and found only in 10 % of cases (3,4). Adrenal bleeding is more frequent in boys than in girls (1). It can be minimal without clinical signs or fulminant with acute adrenal insufficiency. We present a rare clinical case of primary adrenal insufficiency due to bilateral adrenal bleeding in a newborn baby girl treated for severe early jaundice.

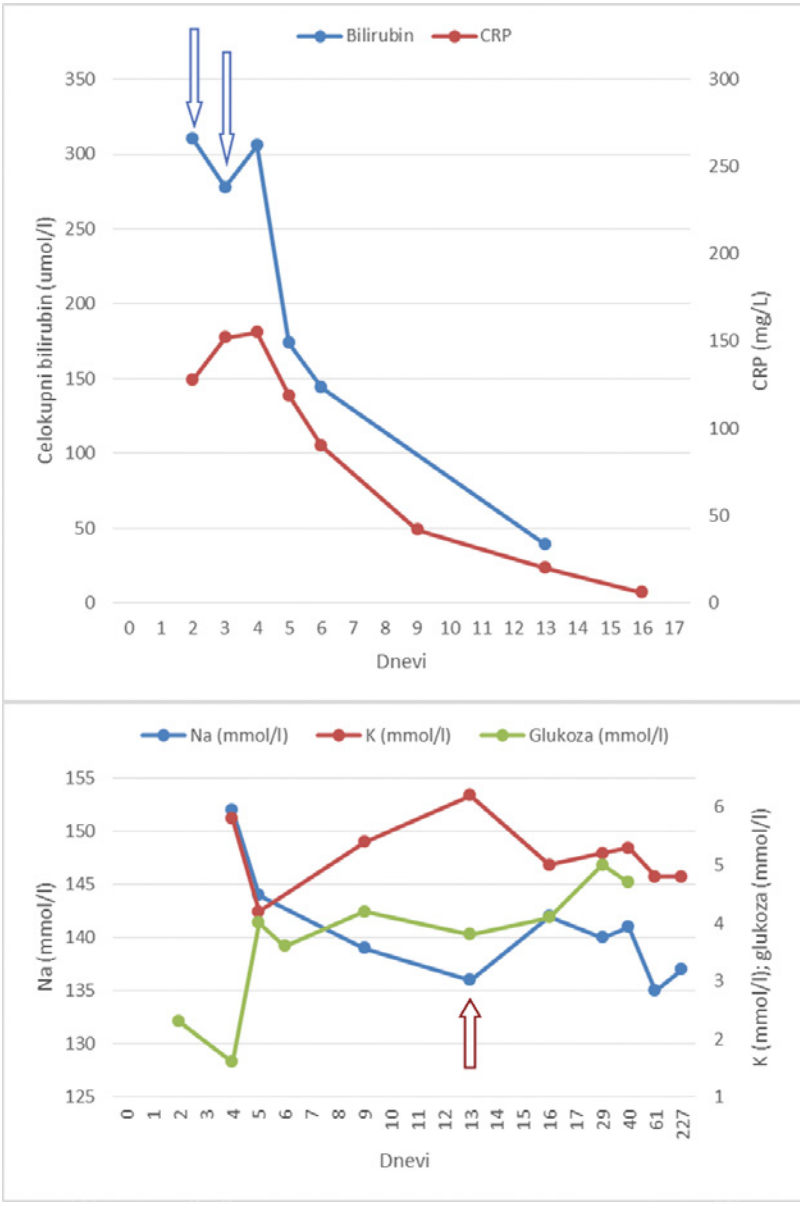

Figure 1: Graphical representation of laboratory concentrations of total bilirubin and C-reactive protein (upper graph), and serum sodium, potassium and glucose concentrations in the newborn and infant at the time of follow-up (the graph below). In the upper graph, the blue arrow indicates the start and discontinuation of antibiotic treatment. The red arrow in the lower graph shows the beginning of hydrocortisone therapy.

2. Clinical case

The baby girl was born as a second child after completed 38th week of gestation with a birth weight of 4410 g (above the 95th percentile), a birth length of 55 cm (above the 95th percentile) and a head circumference of 35 cm (50–90th percentile), and was large for gestational age (LGA). The baby girl's mother subjectively considered the labour not difficult, and rather fast. The Apgar score was 9 and 10 at 1 and 5 minutes after birth, respectively. In the family history, the father and paternal uncle have autoimmune hepatitis. Because of gestational diabetes diagnosed in the first half of pregnancy, the mother was treated with diet, without having to receive insulin.

In the 37th week of pregnancy, polyhydramnios and increased abdominal circumference of the foetus was found on ultrasound (US) examination. On the second day after birth the baby girl's body weight was reduced by 8 %. She became more icteric. Laboratory test results revealed increased C-reactive protein (CRP 123 mg/L) levels, which increased to 152 mg/L on the third day of life; total bilirubin levels were also increased (318 µmol/L). Because of suspected early sepsis in the newborn, the haemoculture test was done in the local hospital, and empirical double antibiotic treatment with ampicillin and gentamicin was started. The baby girl was transferred to the Department of Neonatology, Division of Paediatrics, University Medical Centre Ljubljana on day 3 of life for further treatment.

On admission, she was afebrile, diastolic arterial blood pressure was lower (91/54 mm Hg; 95th percentile/50th percentile) and stabilised after parental hydration. She was irritable, yellowish-pink, without any other pathology found on physical examination. On the first day of hospitalisation, there were occasional reductions in oxygen saturation in arterial blood, but she did not need oxygen supplement in the inspired air. Haemograms and differential blood counts on admission were as follows: haematocrit 0.623, haemoglo-

bin 200 g/L, MCV 114, platelets 128, reticulocytes 7.3 %, leukocytes 11.8 × 109, CRP 155 mg/L. In the peripheral smear, 2 % of non-segmented neutrophils were present, 48 % of segmented neutrophils, 42 % of lymphocytes, 6 % of monocytes and 2 % of eosinophils. Because of hypoglycaemia (1.6 mmol/L), the baby girl needed parenteral glucose replacement (6 mg/kg/min) for 60 hours. With the establishment of enteral feeding, parenteral glucose infusion was gradually reduced, and the serum glucose concentrations normalised.

On admission at the age of three days and clinically present jaundice, the total bilirubin level was increased because of increased indirect bilirubin (306 μmol/L, Figure 1). The mother's blood group was O RhD positive, the baby girl's, determined on plate, was O. Therefore, the blood group incompatibility of the mother and the child was not the cause of severe early jaundice. Searching further for the causes of severe early jaundice – internal bleeding – we performed an US examination of the head that did not show any bleeding, and the US examination of the abdomen, which showed increased adrenal glands in which there was a severely restricted, partially echogenic, mostly liquefied mass – haematoma; in the right adrenal gland it measured 29 × 46 × 39 mm (27 mL) (Figure 2, above), and in the left 38 × 43 × 47 mm (41 mL) (Figure 2, below). Because of indirect hyperbilirubinaemia, the baby girl needed phototherapy for a total duration of 21 hours. Applying appropriate phototherapy, indirect bilirubin levels gradually decreased.

Laboratory tests during hospitalisation showed increased CRP levels which slowly but gradually decreased with double antibiotic therapy (Figure 1). Microbiological investigations (haemoculture, urine culture) did not confirm the infection. Decreasing of CRP levels along with negative microbiological investigation results was too slow, therefore elevated CRP could not be attributed to infection. Apart from transiently higher serum potassium levels (up to 6.2 mmol/L), no electrolyte imbalance was observed. Sodium levels were within the reference range for the baby girl's age (Figure 1), and the levels of other electrolytes were normal (chloride 112 mmol/L, calcium 1.85 mmol/L). All basic blood tests of clotting times were within normal limits.

At lower blood pressure, hypoglycaemia, marginally higher potassium levels, and US finding of bilateral adrenal bleeding, a high-dose adrenocorticotropic hormone (ACTH) test was performed to assess the activity of the adrenal glands. Test results showed a marginally lower basal cortisol level 165 nmol/L (< 200 nmol/L), and ACTH was higher than 17.7 pmol/L (> 6.2 pmol/L) (5). After 60 minutes, cortisol increased suboptimally – 350 nmol/L (< 500 nmol/L). Hydrocortisone therapy was started at the rate of 1.6 mg/kg of body weight or 11 mg/m2. Four months after starting the hydrocortisone therapy, we again performed a high-dose ACTH test after a short-term discontinuation of hydrocortisone treatment. The basal value of cortisol was normal (229 nmol/L), and ACTH was marginally higher (22.2 ppmol/L). After 60 minutes, the cortisol increase was suboptimal – 406 nmol/L. On US examination of the abdomen, a marked decrease in the haematoma size was observed; a large hypoechogenic formation of 13 × 7 × 12 mm was seen in the right adrenal gland (Figure 3 above), and in the left a large formation of similar appearance (10 × 10 × 9 mm) (Figure 3). There were no convincing calcifications seen in the adrenal glands. The baby

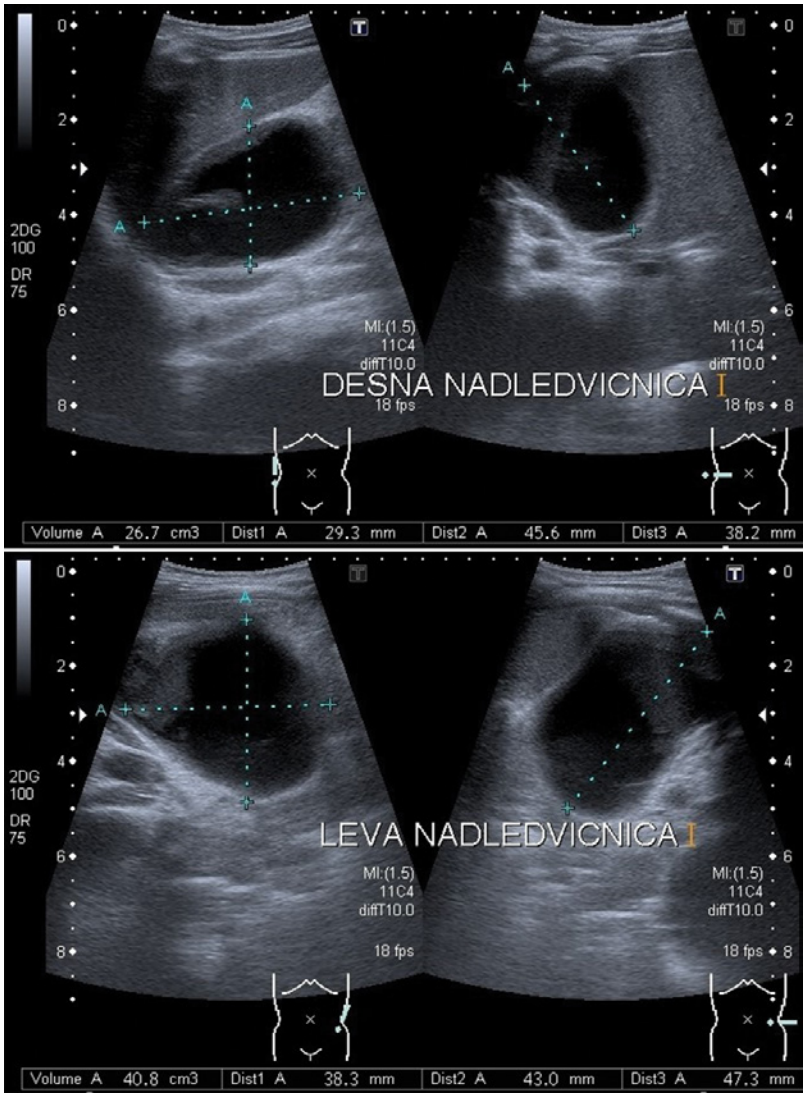

Figure 2: US image of haematoma in adrenal glands at the age of three days (haematoma in the right adrenal gland measures 29 × 46 × 38 mm – upper image, in the left adrenal gland 38 × 43 × 47 mm – lower image).

girl is currently continuing hydrocortisone treatment.

3. Discussion

Neonatal jaundice is a common and important clinical sign of sick newborns. If it occurs within the first 48–72 hours, it is called early, and is most often due to increased bilirubin production. The most common cause of a severe early jaundice is blood group incompatibility between the mother and the child, which causes haemolytic anaemia with hyperbilirubinaemia due to the presence of maternal antibodies that destroy the newborn's erythrocytes (7). In the past the most common cause was the Rh incompatibility of D antigens, but after the introduction of immunoglobulin protection in Rh D negative pregnancies, the most common incompatibility is that of ABO antigens (7). The nonimmune causes of severe early jaundice are the lack of glucose-6-phosphate dehydrogenase, erythrocyte membrane diseases, and haemoglobinopathy (8). If jaundice occurs after 48–72 hours after birth, we call it late jaundice. It is most often associated with slow excretion of bilirubin with or without increased bilirubin production. The most common causes are infections, haematomas, polycythaemia, increased enterohepatic circulation and various metabolic diseases. Early jaundice remains unexplained in 30–40 % of cases (9). Adrenal gland bleeding is a rare cause of early jaundice (3).

There are several theories about the mechanisms causing adrenal bleeding in neonates. In the neonatal period, the adrenal glands are larger in comparison with later periods of life receiving a higher proportion of blood. The conditions that cause hypoxia often lead to adrenal bleeding as hypoxia triggers the activation of the baroreceptor stress response. Hypoxia damages endothelial cells, which increases susceptibility to bleeding. Higher blood volume, body size, and mechanical damage to the endothelium due to hypoxia can pathophysiologically explain the increased risk of bleeding in the neonatal period. Anamnestic data that may indicate the newborn's predisposition to adrenal bleeding are traumatic delivery, being born large for gestational age, diabetes in pregnancy, asphyxia, blood clotting

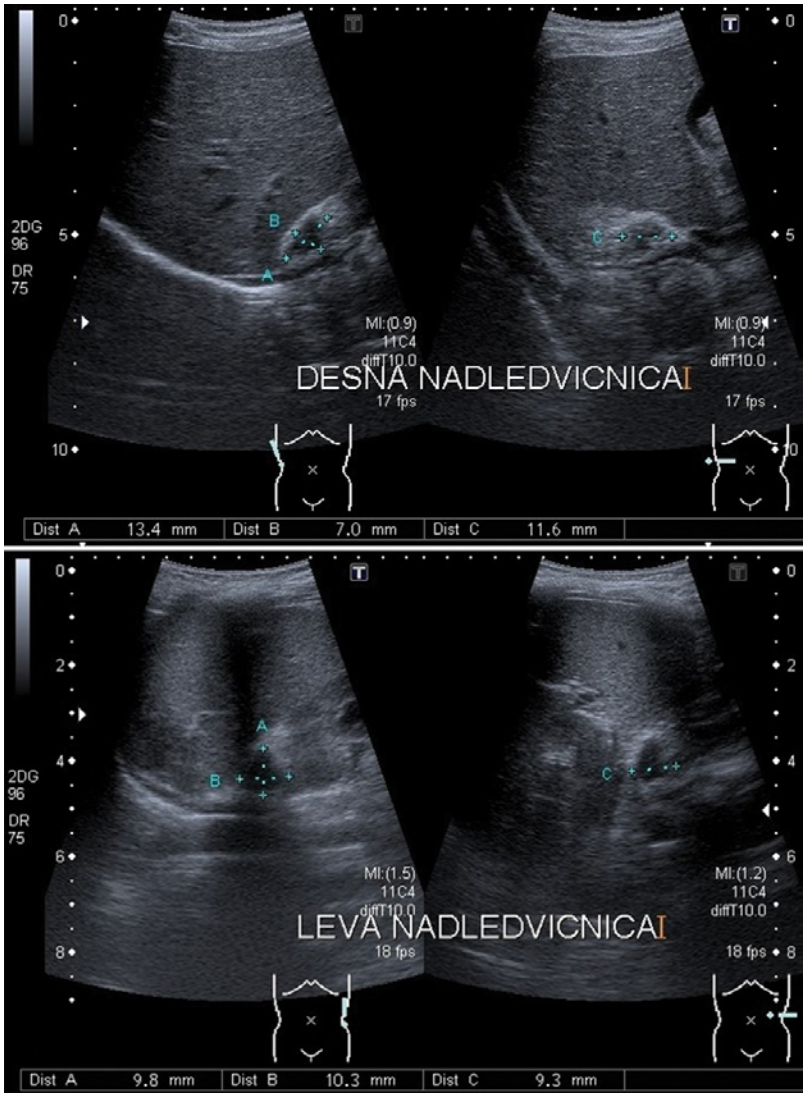

Figure 3: US image of the remnant of haematoma in adrenal glands at the age of four months (the remainder of the haematoma in the right adrenal gland measures 13 × 7 × 12 mm – the upper image, in the left adrenal gland 10 × 10 × 9 mm – the lower image).

disorders, and sepsis. In our clinical case, the newborn was large for gestational age, the labour was fast, the baby girl's mother was diabetic, and due to severe early jaundice and irritability, an early-onset sepsis was suspected. The blood groups of the mother and the newborn were compatible. Therefore, the blood group incompatibility was not likely to be the reason for severe early jaundice. Macrosomia and gestational diabetes are risk factors for traumatic delivery, and subsequent hypoxic injury at birth, which may be the cause of adrenal bleeding. Due to the resorption of haematoma and erythrocyte breakdown, jaundice appears. In addition to adrenal bleeding, neonatal jaundice in our case may partly be explained by polycythaemia during gestational diabetes and haemoconcentration with a decrease in body weight within the first days after birth.

Adrenal insufficiency following adrenal bleeding is a rare condition (10), because adrenal glands are paired organs, rarely damaged to the same extent (11). In the presented newborn, some clinical and laboratory signs of mild adrenal insufficiency were observed. On admission, she had arterial hypotension which was resolved after parenteral hydration. Hypoglycaemia was corrected by parenteral glucose replacement. The blood glucose concentration normalized after adequate feeding was established. Beside acute adrenal insufficiency relative hyperinsulinism may also have contributed to lower blood glucose concentration during gestational diabetes. The baby girl was large for gestational age suggesting that her mother's gestational diabetes was not completely regulated. The electrolyte imbalance, except for the potassium concentration at the upper limit of normal values, was not detected. To assess the adrenal function, we performed a high-dose ACTH stimulation test. The basal cortisol level was lower, and ACTH was higher, which is in line with the primary adrenal disorder (12). When stimulated with ACTH, cortisol did not increase sufficiently. The control high-dose ACTH test, performed at 4-months of age, elucidated high basal ACTH values along with cortisol concentrations at the lower limit, and an insufficient increase in cortisol. The primary adrenal insufficiency in the baby girl was most likely the result of extensi-

ve damage to the tissue of both adrenal glands during perinatal haemorrhage in both adrenal glands (13).

When localized liquid mass in the suprarenal space is detected on US examination, other possible causes should be excluded. Neonatal adrenal bleeding is the most common cause of a liquid change visible by US in the area of adrenal glands, rarer causes being Beckwith-Wiedemann syndrome, neuroblastoma, abscess, hydronephrosis or cystic kidney disease. US scan of bleeding depends on its age. In the early acute phase of bleeding, the adrenal gland is increased exhibiting a homogeneous hyperechogenic pattern. Gradually, the blood is liquefied, within 1–2 weeks the central part of the bleeding becomes extremely hypoechogenic with individual echogenous inclusions. Soon the blood is resorbed, the haematoma becomes smaller, in 4–6 weeks a minimal, echogenic, and partially calcified residual haematoma may remain. There are no specific US signs of adrenal haematoma; however, to confirm the diagnosis, the US image of the reducing change, and the dynamics of changes of US scans as described above are sufficient. In our baby girl, the control US examination of the abdomen showed a convincing decrease in haematomas in both adrenal glands, which excluded other possible causes of localized fluid mass in the adrenal glands. The follow-up of diagnosed adrenal bleeding with US is also important for monitoring possible bleeding complications. In newborns, there is a common association between renal venous thrombosis and adrenal bleeding. Renal vein thrombosis is more often left-sided due to the direct flow of the left adrenal vein into the left renal vein. The occurrence of abscess is also an important complication of adrenal bleeding (14-16).

In our newborn, we observed high CRP concentrations, while the procalcitonin concentration was not increased. Due to the suspicion of early-onset sepsis, the cultures were taken, and empirical double antibiotic therapy was introduced in the regional maternity hospital already. On admission to the Department, the baby girl showed clinical signs of irritability and occasional falls in the arterial blood oxygen saturation. High values of inflammatory markers indicated the need for continuation of dual antibiotic therapy. The microbiological cultures did not prove an infectious cause; also the laboratory findings did not show the typical course of infection: CRP remained elevated despite antibiotic therapy, and procalcitonin was always within the normal limits, other haematological markers, typical for the neonatal period – thrombocytopoenia, leukopoenia, neutropoenia – were not present. After 6 days of treatment, the antibiotic therapy was discontinued. With unproven infective cause of increased inflammatory markers, possible non-infectious causes of elevated CRP were considered. CRP is an inflammatory marker synthesised in hepatocytes; its concentrations remain high throughout the course of inflammation or tissue damage. It is important for the assessment of disease activity or tissue damage (17). Non-infectious causes of elevated CRP are premature rupture of the membranes, intraventricular bleeding, pneumothorax, mother's fever during labour, prolonged labour, perinatal asphyxia, aspiration of meconium, surfactant delivery and tissue damage (18). After having excluded infection as a probable cause of elevated CRP, the damage of adrenal tissue was considered. A relative persistence of elevated inflammatory markers for several days after cessation of antibiotic therapy, negative microbi-

ological findings, and low procalcitonin concentrations, procalcitonin being more sensitive inflammatory marker of infection than CRP, they all spoke in favour of this possibility. An additional confirmation of our hypothesis was also functional adrenal insufficiency due to the reduced functional glandular tissue.

4. Conclusions

Adrenal bleeding is a possible, although a rare cause of a severe early jaundice in the newborn (1). In the differential diagnosis an US examination of the abdomen should be performed to confirm the presence of bleeding, and to monitor resorption and possible complications (19). The damage to the adrenal glands after bleeding is rarely so extensive that a functional disorder with primary adrenal insufficiency occurs. Nevertheless, in the case of unexplained severe early neonatal jaundice with other more frequent causes of early jaundice excluded, a bilateral adrenal bleeding should be considered. When both the clinical picture and laboratory findings support the diagnosis of acute adrenal insufficiency, hormonal testing should also be performed to confirm the diagnosis. Unrecognized and incorrectly treated acute adrenal failure is a life-threatening condition. Its identification is therefore essential for the recovery and long-term outcome of treatment.

The parents of the child agree with the publication of the article describing the clinical case of their baby girl.

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