Adrenal bleeding in neonates: report of 37 cases*

Nihal Demirel[1], Ahmet Yağmur Baş[1], Ayşegül Zenciroğlu[2], Yasemin Taşcı-Yıldız[3]

[1]Department of Neonatology, Ankara Zübeyde Hanım Etlik Maternity and Gynecology Training and Research Hospital, and Departments of [2]Neonatology, and [3]Radiology, Dr. Sami Ulus Children's Hospital, Ankara, Turkey

SUMMARY: Demirel N, Baş AY, Zenciroğlu A, Taşcı-Yıldız Y. Adrenal bleeding in neonates: report of 37 cases. Turk J Pediatr 2011; 53: 43-47.

Adrenal hemorrhage is more common in neonates than in children or adults. The incidence of detected cases ranges from 1.7 to 2.1 per 1000 births. Because adrenal bleeding may remain asymptomatic, the real occurrence is probably higher. In this retrospective study, we evaluated epidemiologic properties, risk factors and clinical presentations of adrenal hemorrhage in 37 term newborn babies diagnosed as adrenal hemorrhage with abdominal ultrasonography between January 2003 and July 2007 in Dr. Sami Ulus Children's Hospital Neonatal Intensive Care Unit (NICU). We also evaluated the role of adrenal hemorrhage among the etiologic factors of unexplained jaundice. Abdominal ultrasonography was applied to 2280 newborns, and 37 newborns (25 male, 12 female) were diagnosed as adrenal hemorrhage (1.6%). The male/female ratio was 2.08. The average age and birth weight at admission were 4.9 ± 0.3 days and 3333 ± 939 g, respectively. Adrenal hemorrhage was right-sided in 24, left-sided in 9 and bilateral in 4 newborns. Resolution time of adrenal hemorrhage was a minimum of 3 months, maximum of 9 months in ultrasonographic follow-up. The most common clinical feature in infants with adrenal hemorrhage was jaundice, which was observed in 67.6% of cases (n=25). We advise that, in cases of hyperbilirubinemia of unknown etiology, adrenal hemorrhage must be kept in mind. We recommend abdominal ultrasonography for further evaluation.

Key words: adrenal hemorrhage, hyperbilirubinemia, abdominal ultrasonography, adrenal bleeding, newborn.

The fetal and neonatal adrenal glands are relatively large in size and are more vascularized than later in life, which may predispose to adrenal bleeding[1]. Neonatal adrenal hemorrhage is frequently associated with large fetal size, birth trauma owing to difficult labor or delivery, perinatal asphyxia, septicemia, or coagulation defects[2]. The clinical presentation varies from asymptomatic minimal bleeding, to fulminant hemorrhage with resultant death from exsanguination or adrenal insufficiency[3]. The frequent clinical manifestations are mild anemia, unexplained jaundice and an abdominal mass[4]. Abdominal sonography facilitates the diagnosis of adrenal hemorrhage particularly when the clinical presentation is subtle[5].

The aim of this study was to evaluate epidemiologic properties, risk factors and clinical presentations of term newborn babies with adrenal hemorrhage. We also investigated the role of adrenal hemorrhage in the etiology of unexplained jaundice.

Material and Methods

In this study, we reviewed the medical records of patients with adrenal hemorrhage in Dr. Sami Ulus Children's Hospital Neonatal Intensive Care Unit (NICU) between 1 January 2003 and 30 July 2007. Infants with congenital/chromosomal anomalies or who were referred to other centers and preterm babies were excluded from the study.

The following data were recorded:

Neonatal and maternal characteristics: Birth weight, type of delivery, gender, age on admission, complaint on admission, need for resuscitation in delivery room, and presence

*Presented as a poster at the 3rd Europaediatrics Congress, İstanbul, 2008.

of perinatal asphyxia, birth trauma, maternal diabetes, and gestational hypertension.

Clinical features: Fever, hypothermia, tachypnea, cyanosis, pallor, hypovolemic shock, jaundice, abdominal mass, and hemorrhage in other regions of the body.

Laboratory evaluation: In our NICU's protocol, abdominal sonography is performed in infants with perinatal asphyxia, abdominal distention, neonatal sepsis, acute renal failure, unexplained jaundice, and in infants of diabetic mothers.

Complete blood cell count and differential were done routinely on admission in all infants. Anemia is defined by a hemoglobin (Hb) value that is more than two standard deviations below the mean for age[6]. Serum total and indirect bilirubin levels, reticulocyte count and blood group antigen analysis were evaluated in all infants with jaundice, and subgroup antigens, glucose-6 phosphate-dehydrogenase (G6PD) enzyme levels, thyroid function tests, and urine cultures were evaluated in infants with prolonged jaundice during their hospitalization.

Serum urea, creatine, sodium, potassium, glucose, C-reactive protein, and coagulation tests were studied in infants who were detected as having adrenal hemorrhage by abdominal sonography. Coagulation tests included bleeding time, prothrombin time (PT), partial thromboplastin time (PTT), protein C, protein S, antithrombin III levels, and activated protein C resistance test.

Perinatal asphyxia was defined based on an Apgar score of 3 for >5 min, and/or neurologic manifestations in the immediate postnatal period, including seizures, hypotonia, coma, or hypoxic ischemic encephalopathy (HIE), and evidence of multiorgan system dysfunction[7].

Phototherapy was initiated and exchange transfusion was performed according to the guidelines of the American Academy of Pediatrics. Prolonged jaundice was defined as persistence of indirect hyperbilirubinemia beyond two weeks[8].

Abdominal sonography was performed by trained radiologists. In cases with adrenal hemorrhage, the first ultrasonographic follow-up examination was performed 15 days later. Afterwards, ultrasonographic examinations were performed every month for the first three months and every three months thereafter.

Results

During the study period, 3470 term infants were admitted to our NICU. Abdominal sonography was applied to 2280 newborns, and 37 newborns were diagnosed to have adrenal hemorrhage (1.6%).

Among these 37 newborns, 25 were male and 12 were female. The average age and birth weight on admission were 4.9 ± 0.3 days and 3333 ± 939 g, respectively. Neonatal and maternal characteristics of infants with adrenal hemorrhage are presented in Table I and clinical and laboratory findings are presented in Table II.

The most common clinical feature in infants with adrenal hemorrhage was jaundice, which was observed in 67.6% of cases (n=25). Five of them presented with prolonged jaundice. Exchange transfusion was performed in six of the infants with jaundice due to indirect hyperbilirubinemia (IHB), and no other explanation was found for these high bilirubin levels.

Table I. Newborn and Maternal Characteristics of Infants with Adrenal Hemorrhage

Number of patients	37	%
Male	25	67.6
Gestational hypertension	2	5.4
Maternal diabetes	5	13.5
Spontaneous vaginal delivery	34	91.9
Cesarean section	3	8.1
Traumatic delivery	4	10.8
Perinatal asphyxia	4	10.8
Resuscitation in delivery room	7	18.9
Large for gestational age	8	21.6

Table II. Clinical and Laboratory Findings of Infants with Adrenal Hemorrhage

Number of patients	37	%
Jaundice	25	67.6
Scrotal hematoma	1	2.7
Subgaleal hemorrhage	1	2.7
Palpable abdominal mass	1	2.7
Adrenal insufficiency	1	2.7
Anemia on admission	1	2.7
Asymptomatic	7	18.9
Right-sided adrenal hemorrhage	24	64.9
Left-sided adrenal hemorrhage	9	24.3
Bilateral adrenal hemorrhage	4	10.8

In the study period, 957 newborns were hospitalized in our neonatology unit due to jaundice and treated with either phototherapy or exchange transfusion. In the etiology of hyperbilirubinemia, blood group incompatibility (ABO, Rh or subgroup) was detected in 362 newborns, urinary tract infection in 12, hypothyroidism in 8, hereditary spherocytosis in 1, and G6PD deficiency in 1 newborn(s). In 114 cases, IHB was found to be related with polycythemia, cephalic hematoma and/or excessive bruising and breastfeeding jaundice. Among the rest of the neonates (n=459) with unexplained jaundice, 25 were diagnosed as adrenal hemorrhage (5.4%).

In the cases of adrenal hemorrhage, 4 patients were diagnosed as HIE stage III. Adrenal insufficiency was observed in 1 newborn and disseminated intravascular coagulation (DIC) was observed in 2 newborns with HIE stage III. Hypothermia, tachypnea, cyanosis, pallor, and hypovolemic shock were present in the patients with DIC as well as prolonged PT and PTT. The other coagulation tests were all normal in the rest of the patients in our study group.

Adrenal hemorrhage was right-sided in 24 newborns, left-sided in 9 and bilateral in 4. Minimum and maximum adrenal hemorrhage sizes were 26x27x23 mm and 56x48x51 mm, respectively.

Resolution time of adrenal hemorrhages was a minimum of 3 months and maximum of 9 months in ultrasonographic follow-up. Calcifications in adrenal glands were observed in 12 newborns after resolution of hemorrhages. Three newborns with HIE stage III died with adrenal hemorrhage.

Discussion

Neonatal adrenal hemorrhage is more common than previously suspected, and the incidence ranges from approximately 1.7 to 2.1 per 1000 births[9]. In this study, 37 term infants with adrenal hemorrhage diagnosed by abdominal sonography over a period of 3.5 years reflected an incidence of 1.6%. Our observation supported that this is not a rare problem. However, adrenal hemorrhage was not considered as the primary diagnosis in any of the cases before abdominal sonography.

Males are affected more frequently than females, and the right-side is involved three to four times more than the left; it is bilateral in 10% to 15% of cases[10]. In this study, consistent with the previously reported articles, we found male predominance and right-sided localization. The mechanism for the right-sided predilection is presumed to be secondary to compression of the adrenal gland between the liver and the spine. Since the right adrenal vein usually drains directly into the inferior vena cava, compression is likely to induce venous pressure changes[11].

The etiology of adrenal hemorrhage is not known. This condition likely has a multifactorial cause rather than a single explanation. Any condition leading to hypoxia may lead to shunting of blood flow to vital organs. Furthermore, hypoxia causes damage to the endothelial cells, making them more prone to hemorrhage. The relatively large size and extensive vascularity of the adrenal gland may result in vulnerability to mechanical changes in venous pressure during delivery[3]. Predisposing factors include difficult labor or delivery, high birth weight, asphyxia, septicemia, and hemorrhagic disorders[12]. DeSa

and associates[13] reported histologic changes consistent with infarction in a series of 122 cases, suggesting a hypoxic-ischemic event with subsequent reperfusion injury as the basis for adrenal hemorrhage.

In eight cases of this study, history and clinical findings of traumatic delivery and perinatal asphyxia were present. Thus, ischemia and reperfusion injury may be the potential mechanism of adrenal hemorrhage in these cases. However, the causes of the adrenal hemorrhage in the others were unclear.

The clinical presentation is variable and depends on the volume of hemorrhage. Usually, if bleeding is scarce or moderate, the blood remains in the capsule; however, a larger amount of blood can pass into the peritoneal cavity or into the retroperitoneal space. The symptoms in such cases are anemia, hemoperitoneum, palpable abdominal mass, and persistent jaundice. Retroperitoneal blood leakage may present as scrotal hematoma if the processus vaginalis is patent, mimicking a condition of acute scrotal pathology[3,10]. The initial presentation in one of our patients was heralded by discoloration of the scrotum. This occurred with no history of trauma or signs of testicular torsion.

Adrenal hemorrhage should be considered in the differential diagnosis of abdominal flank masses. It may be extremely difficult to differentiate adrenal hemorrhage from renal conditions such as hydronephrosis, cystic renal disease, vascular thrombosis, or a neuroblastoma. Abdominal sonography may help to differentiate a hemorrhage from neuroblastoma. Serial ultrasonographies will show an interval of resolution of adrenal hemorrhage but persistence or enlargement of adrenal neoplasm[3]. One of the infants with large adrenal hemorrhage in our study was referred to our hospital with the diagnosis of neuroblastoma.

In the newborn period, unconjugated hyperbilirubinemia is a common, multifactorial condition and is associated with a variety of physiologic and pathologic conditions[14]. The most known pathologic causes of neonatal hyperbilirubinemia include ABO incompatibility, Rh isoimmunization, infection, excessive bruising, presence of maternal diabetes, polycythemia, G6PD deficiency, pyruvate kinase deficiency, and congenital spherocytosis. Extravascular blood collections also lead to hyperbilirubinemia. Adrenal hemorrhage may lead to unexplained jaundice from reabsorption and breakdown of red blood cells in the hematoma.

Twenty-five of 37 cases (75.7%) with adrenal hemorrhage in our study were admitted to our unit with hyperbilirubinemia and the ones with known etiologies of hyperbilirubinemia were excluded. Adrenal hemorrhage was not considered as the primary diagnosis in any of the cases before abdominal sonography.

Adrenal insufficiency has rarely been associated with adrenal hemorrhage even when it is severe[5]. A possible explanation for this observation is that even with large hemorrhage, both glands are unlikely to be affected to the same extent[3]. In our study, we observed clinical or laboratory findings of adrenal insufficiency in only one patient, who was diagnosed as HIE stage III and presented with hypotension.

In conclusion, this is one of the largest series of adrenal hemorrhage and highlights the diverse associated clinical presentations. Abdominal sonography is the modality of choice for initial diagnosis and follow-up of neonatal adrenal hemorrhage, and conservative management is the mainstay of treatment. Primary coagulation disorders had no role in the etiology in our study. We advise that, in cases of hyperbilirubinemia with unknown etiology, adrenal hemorrhage must be kept in mind. We recommend abdominal ultrasonography for further evaluation.

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