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EDİTÖRE MEKTUP / LETTER TO THE EDITOR

Bilateral adrenal hemorrhage with signs of adrenal insufficiency in the first days of life

Yaşamın ilk günlerinde adrenal yetmezlik belirtileri olan bilateral adrenal kanama

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To the Editor,

Adrenal insufficiency is often a temporary process when it is associated with adrenal hemorrhage. Many cases of adrenal hemorrhage are asymptomatic. Although rare, persistent adrenal insufficiency may occur in patients with large or bilateral adrenal hemorrhage. The large size and increased vascularity of the adrenal glands and and hypoxia-associated damaged endothelial cells can cause adrenal hemorrhage[1].

The incidence of adrenal hemorrhage (AH) in newborns is reported to be between 1.7 and 3 per 1000 live births. However, in retrospective studies examining abdominal ultrasonography (USG) screening in newborns, high rates such as 16-29 in 1000 live births were also reported[2]. The vast majority of AH is asymptomatic and is detected incidentally. Adrenal hemorrhage often occurs in term and male infants[4]. The clinical feature varies from asymptomatic minimal bleeding to severe bleeding and adrenal insufficiency (AI), which can leads to death[3,4]. Frequent clinical manifestations are mild anemia, unexplained jaundice and abdominal mass. When unilateral bleeding is severe, shock is observed. There may be signs of hypocortisolemia in the bilateral AH cases. Patients usually recover rapidly and those who progress to adrenal insufficiency and need treatment are rare. Because even the presence of 10% tissue that produces functional cortisol is sufficient to prevent AI. Adrenal insufficiency is observed when AH is bilateral and findings are usually detected in the first week of life. Some cases may take longer time to recover[5]. Here, the case bilateral adrenal bleeding was shared with the literature, due to this case showed signs of adrenal insufficiency in the first days of life.

A baby boy-from the first pregnancy of the 26-year-old mother-who was delivered by emergency c-section at the 34th gestational week due to acute fetal distress. The Apgar scores were 7 (at 1 min) and 8 (at 5 min). The mother had been using insulin because of type 1 diabetes mellitus for 14 years and her blood glucose were regulated during pregnancy. The pregnancy was uneventful except diabetes. Nasal Continuous Positive Airway Pressure (NCPAP) was applied to the baby due to the presence of respiratory distress. The baby's birth weight (2,700 kg), length (44 cm) and head circumference (31 cm) were appropriate for gestational age. There were no features other than findings of respiratory distress in physical examination. Respiratory distress were improvement. However, at the 6th hour of hospitalization, the potassium that was measured was found high (9,1 mmol / L) and sodium was low (127 mmol / L). No hypoglycaemia was observed. After the treatment of hyperpotasemia, potassium was reduced to 6.3 mmol / L. The possible causes were examined; increased in alanine transaminase (115 U / L), aspartate transaminase (162 U / L), bilirubin, creatinine (1,65 mg / dL) and a slight decrease in the

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hemoglobin (13,6 g / dL) value were noted. On the second day, phototherapy was started due to jaundice. Although the baby received phototherapy, bilirubin levels decrease was slower than expected. Direct coombs test negative and blood groups of mother and baby were similar. Procalcitonin value was slightly high and empiric treatment with ampicillin and gentamicin was started.

Cranial and abdominal USG was performed on the baby who had acute fetal distress in the history. Cranial USG was normal. An image compatible with bilateral adrenal bleeding was observed in abdominal USG (Fig. 1A). Abdominal magnetic resonance imaging (MRI) was also performed to exclude other possible causes, and the result was reported as bilateral surrenal bleeding. (Fig. 1B). Electrolyte imbalance and / or hypoglycemia did not occur again in the follow-up of the patient. On the 6th day of life, the skin color, breast areola and scrotum were noticed to be slightly darker than before (Fig. 2). Test for diagnosis AI were done. Plasma renin activity, aldosterone, 17-hydroxyprogesterone, dehydroepiandrosterone, dehydroepiandrosterone sulfate, thyroid stimulating hormone and free throxine were normal. However, cortisol was at the lower limit (4.2 µg / dL) and ACTH was high (347 ng / L), and the patient underwent conventional high-dose ACTH stimulation test (250 µg / m^2 intravenous). There was no expected increase in cortisol value (6,9 ve 6,6 µg/dL in 30th and 60th minutes, respectively). The baby was diagnosed with AI and hydrocortisone treatment (15 mg / m^2 / day, orally) was started.

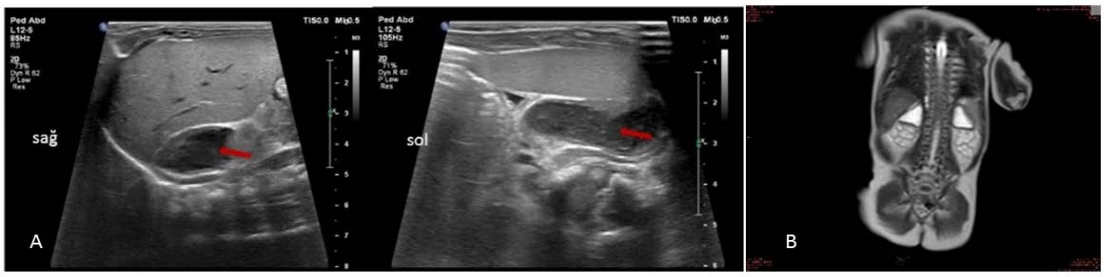

Figure 1. A: In abdominal USG, heterogeneous-hyperechoic apperance with thick walls in both adrenal glands (21x24 mm on the right and 21x20 mm on the left), B: In MRI, signal changes compatible with bilateral subacute hemorrhage in adrenal glands (Hyperintense in T2A-weighted coronal section in axial plane).

Figure 2. Skin color, breast areola were noticed to be slightly darker (since the family did not allow the use of pictures of genital area for publication, the scrotal hyperpigmentation image was not shared).

The baby, who had no other problems was discharged on the 18th day of life. In the control five days later, his blood glucose and electrolytes were normal and cortisol was 1.2 µg / dL and ACTH 20.4 ng / L. The patient was followed up by monthly USG, weekly blood sugar and electrolyte control. Ultrasonographic findings in 3rd month of life were normal. Hydrocortisone treatment was reduced by performing high-dose ACTH stimulation test in the 5th month of life. Written consent was obtained from the family to share the case in a scientific area.

The etiology of AH is unclear and possibly multifactorial. Any condition that causes hypoxia can lead to shunting of blood flow to vital organs. The relatively large size and wide vascularity of the adrenal gland tends to be injured during labour due to mechanical changes in venous pressure[4]. DeSa et al.[6] reported histological changes compatible with infarction in 122 cases and showed reperfusion injury after a hypoxic-ischemic event as the basis of adrenal bleeding. 10% of AH cases are bilateral. 75% of the unilateral cases are on the right adrenal gland due to the compression of the adrenal gland between the

liver and the spine and the venous drainage of the right adrenal gland directly into the inferior vena cava[5]. Most cases do not cause impairment of adrenal function[4,7].

Adrenal bleeding can be acquired (Waterhouse–Friderichsen syndrome, primary antiphospholipid syndrome and anticoagulation), traumatic or idiopathic[7]. Predisposing factors include difficult birth, high birth weight, asphyxia, septicemia, hemorrhagic disorders, thrombocytopenia, hypotrombinemia, disseminated intravascular coagulation and Factor V Leiden deficiency[8]. The largest study of newborn cohort with adrenal bleeding reported that the two most common variables were fetal acidemia (31%) and macrosomia (22%)[8].

In adrenal glands, hematoma with a calcified center is detected incidentally by radiological examination or autopsy in older infants and children, suggesting that not all AH is fatal[8]. The strong regenerative capacity of the adrenal gland is the reason for the late onset of the findings[8]. The presence of minimally functioning residual tissue is sufficient to prevent adrenal insufficiency. Even with bilateral bleeding, it is unlikely that both glands will be affected equally[4]. Most bleeding is subcapsular, the glucocorticoid-producing cortex is separated, which explains the rare occurrence of the Addisonian crisis. Demirel et al.[3] reported that 37 of 2280 babies who underwent USG had adrenal bleeding (1.6%), two thirds of cases was male, the most common clinical finding was jaundice (67.6%), 25 (5.4%) of 459 jaundice cases with no other cause had adrenal bleeding and there were no other reasons to explain indirect hyperbilirubinemia, in six of the babies that require blood transfusion, and the time until the resorption of bleeding varied between 3-9 months. In a different study, the mean recovery time was reported as approximately 18 weeks[2].

The clinical picture is variable and depends on the bleeding volume. Usually, if the bleeding is mild, the blood remains in the capsule; however, more blood may pass into the peritoneal cavity or retroperitoneal space. In such cases, the symptoms are anemia, hemoperitoneum, palpable abdominal mass and jaundice. If processus vaginalis is patent, retroperitoneal blood leakage may emerge as a scrotal hematoma, mimicking acute scrotal pathology.

The most accurate diagnostic test is the conventional high-dose ACTH stimulation test[8]. However, since there may still be functional glucocorticoid producing tissue, a false negative result may occur for the AI if it is performed close to the period in which bleeding is active. Velaphi et al.[4] reported that a newborn with bilateral involvement who presented with hypotension passed the ACTH stimulation test performed on the fifth day postnatal. Klemm et al.[9] discussed several children presenting with circulatory collapse and severe salt loss due to AH, one of which was reported to initially fail ACTH stimulation test but passed at two months of age.

Most neonatal suprarenal masses are diagnosed as congenital neuroblastoma (NBL) or adrenal bleeding. Approximately 50% cases of NBL are detected in children under two years of age, and the adrenal gland is the most common primary site). Bilateral involvement of the adrenal glands is observed in less than 10% of cases with NBL, may occur with synchronous development or metastatic spread of the tumor.

Some AH cases may need glucocorticoid and / or mineralocorticoid therapy. Long-term hydrocortisone therapy should not have a serious suppressive effect on the subsequent function of the hypothalamo-pituitary-adrenal axis. Therefore, it is recommended to withdraw this treatment with clinical or sonographical healing. In the literature, it is emphasized the importance of performing serial USG follow-up and exhibiting a non-invasive attitude, avoiding an early surgical approach.

In conclusion, in our case who had acute fetal distress history, creatinine and transaminase elevation and, poor organ perfusion, AI findings were observed in the first hours of life. Due to the jaundice not giving the expected response to treatment, skin darkening and the presence of electrolyte disorder observed on the first day, AI was suspected and the diagnosis was confirmed by USG. Abdominal USG is the preferred method for initial diagnosis and follow-up. It was emphasized that the importance of considering AH when evaluating the newborn for shock and investigating jaundice of unknown origin. Also, it was emphasized adrenal insufficiency is often temporary when it is associated with AH and in the absence of an infectious etiology and although rare, permanent adrenal insufficiency may be observed in cases of extremely bilateral adrenal bleeding.

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