ORİJİNAL ARAŞTIRMA ORIGINAL RESEARCH

DOI: 10.5336/medsci.2022-87999

Management of Neonatal Adrenal Masses: A Single Center Experience: A Retrospective Study

Neonatal Sürrenal Kitlelerin Yönetimi: Tek Merkez Deneyimi: Retrospektif Çalışma

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This study was presented as an oral presentation at 38th National Congress of Pediatric Surgery, November 25-28, 2021, Antalya, Türkiye.

ABSTRACT Objective: Adrenal hemorrhage in newborns is a rare condition with a frequency of 0.2-0.55%. Various risk factors have been reported besides asphyxia resulting from sepsis, coagulation disorders and traumatic delivery. In this study, we aimed to evaluate the results of our neonatal cases who were followed-up and treated due to adrenal hemorrhage/mass. **Material and Methods:** Patients followed-up(neuroblastoma follow-up protocol)/operated due to adrenal mass between 2007-2021 were retrospectively analyzed. Gender, diagnosis age-type, laterality data, laboratory-ultrasound(US) findings were recorded and examined. **Results:** Along 14 years, two patients with bilateral renal hypoplasia of 44 patients who were evaluated with the preliminary diagnosis of adrenal mass were excluded, so 42 patients were included. Eighteen (42.9%) patients were male, 24 (57.1%) were female, 7 were antenatally-diagnosed, mean age of diagnosis was 11 days in those diagnosed-postnatally. 23 had right, 13 had left, and 6 had bilateral surrenal masses. 38 were cystic, 7 were semisolid, 3 were solid. On the first US, the mean mass size was 34x23mm-the mean mass volume was 12mL. The mean mass size was 31x19mm-the mean mass volume was 8mL in the third month. Urine vanilla mandelic acid levels were normal in all patients. In follow-up, three patients were operated because they had solid lesion size over 16mL. One of them underwent pyeloplasty due to ureteropelvic junction obstruction, two had bening pathology. **Conclusion:** Differential diagnosis between neonatal neuroblastoma and adrenal hemorrhage can be difficult. Follow-up with US-Doppler US and tumor markers is useful and the most reliable method in distinguishing neuroblastoma and adrenal hemorrhage.

Keywords: Neonatal; hemorrhage; neuroblastoma

ÖZET Amaç: Yenidoğanda adrenal kanama %0,2-0,55 sıklıkta nadir görülen bir durumdur. Sepsis, pıhtılaşma bozuklukları ve travmatik doğum nedeniyle oluşan asfiksinin yanı sıra çeşitli risk faktörleri bildirilmiştir. Bu çalışmada, adrenal hemoraji/kitle nedeniyle takip ve tedavi edilen neonatal olgularımızın sonuçlarının değerlendirilmesi amaçlandı. **Gereç ve Yöntemler:** 2007-2021 yılları arasında sürrenal kitle nedeniyle nöroblastom takip protokolüne göre takip ve tedavi edilen olgular retrospektif olarak incelendi. Hastaların cinsiyet, tanı yaşı ve şekli, lezyon tarafı verileri ve laboratuvar-ultrason bulguları kayıtlanarak analiz edildi. **Bulgular:** On dört yılda sürrenal kitle ön tanısı ile değerlendirilen 44 hastadan 2'sinde bilateral renal hipoplazi tespit edilmiş olması nedeniyle 42 hasta çalışmaya dâhil edildi. Olguların 18'i (%42,9) erkek, 24'ü (%57,1) kız olmak üzere 7'si antenatal tanılıydı ve postnatal tanı konulanların ortalama tanı yaşı 11 gündü. 23'ünde sağ, 13'ünde sol, 6'sında ise bilateral sürrenal kitle tespit edildi. Kırk iki hastada toplam 48 sürrenal kitlenin 38'i kistik, 7'si semisolid, 3'ü ise solid yapıdaydı. İlk ultrasonda ortalama kitle boyutu 34x23 mm-ortalama kitle hacmi 12 mL olarak hesaplandı. Üçüncü ay ultrasonlarında ortalama kitle boyutu 31x19 mm-ortalama kitle hacmi 8 mL bulundu. İdrar vanilmandelik asit düzeyi tümünde normaldi. Takiplerinde solid lezyon boyutu 16 mL üzerinde seyreden 3 olgu opere edildi; 1'inde üreteropelvik bileşke obstrüksiyonu nedeniyle pyeloplasti yapılırken, diğer 2'sinde patoloji benign şeklinde raporlandı. **Sonuç:** Yenidoğanda sürrenal lezyonlarda nöroblastom ve adrenal kanama ayırıcı tanısı güçtür. Tümör belirteçleri ile birlikte ultrason ve Doppler ultrason ile lezyon boyutlarının ve kanlanmasının takip edilmesi, nöroblastom ve adrenal kanamayı ayırt etmede en güvenilir yöntemdir.

Anahtar Kelimeler: Neonatal; hemoraji; nöroblastom

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Peer review under responsibility of Turkiye Klinikleri Journal of Medical Sciences.

Received: 05 Jan 2022 ***Received in revised form:*** 23 Mar 2022 ***Accepted:*** 25 Mar 2022 ***Available online:*** 01 Apr 2022

Adrenal hemorrhage in newborns is a rare condition with a frequency of 0.2-0.55%.[1] In neonates, the large size and increased vascularity of the adrenal glands may cause them to be sensitive to mechanical compression and to changes in venous pressure during delivery.[2] In addition, any factor that causes hypoxia can result in a redistribution of blood to the central nervous system, heart, and adrenal glands. Damaged endothelial cells due to increased pressure due to congestion and hypoxia can cause adrenal hemorrhage.[1,2] In addition to birth asphyxia, various risk factors such as sepsis, coagulation disorders, traumatic birth and perinatal injuries have been reported.[2]

The most common adrenal masses in pediatric cases are neuroblastoma and pheochromocytoma of the adrenal gland arising from the neural crest. Neuroblastoma constitutes the leading extracranial solid tumor in pediatric cases and is responsible for 15% of tumor-related deaths.[3] The most important issue in the suspicion of bleeding, especially in unilateral cases, is to distinguish these hemorrhagic lesions from neuroblastoma.[1] Differential diagnoses of lesion near the adrenal gland include adrenal cyst, adrenal abscess, other solid tumors, congenital adrenal hyperplasia, pulmonary sequestration, bronchogenic cyst, enteric cyst, splenic cyst, and cyst lymphangioma.[1]

In this study, it was aimed to evaluate the final results of our newborn cases who were followed up and treated in terms of hemorrhage or neuroblastoma due to adrenal mass.

MATERIAL AND METHODS

The cases that were followed up and treated according to "The Neuroblastoma Follow-up Protocol" in the Pediatric Surgery Clinic of a tertiary center due to adrenal mass between 2007 and 2021 were analyzed retrospectively with the approval of the Zeynep Kamil Women and Children Diseases Training and Research Hospital Clinical Research Ethics Committee dated July 8, 2020 and numbered 139 and conducted in accordance with the principles set forth in the Helsinki Declaration. Informed consents of all patients were obtained from their legal representatives.

Patients' gender, birth weight, gestational week, type of delivery, age at diagnosis, type of diagnosis (antenatal or postnatal), lesion side, laboratory findings, mass sizes and volumes measured in the first ultrasound (US), arterial blood pressure measurements, mass sizes and volumes measured in the third month US, the nature of the lesion (cystic-semisolid-solid) and blood flowing of lesion with Doppler US, the presence of calcification in the lesion, the pathology results of the operated patients were loaded into the SPSS-20 (IBM Corp., Armonk, NY, USA) statistical program and descriptive distributions were analyzed.

RESULTS

Because bilateral renal hypoplasia was detected in two of 44 patients who were evaluated with a preliminary diagnosis of adrenal mass in fourteen years, 42 patients were included in the study. Eighteen (43%) of the cases were male, 24 (57%) were female, and 7 (17%) were antenatally diagnosed. The mean age at diagnosis of those diagnosed postnatally was 11 days (1-86 days).

Thirty five (83%) were born with normal spontaneous vaginal delivery and 7 (17%) were born with cesarean/section. Postpartum clavicle fracture was detected in 2 patients, while one patient with breech presentation had perineal hematoma. Average birth weight was 3,744±405.98 g (2,800-4,950 g), and the mean gestational age was 38.4±1.23 weeks (36-41 weeks). Phototherapy was used in 19 (45%) patients for jaundice, 2 (4.8%) patients required glucocorticoid therapy due to hypoglycemia. When the patients were first diagnosed, the mean hospital stay was 3.6±2.9 days (2-15 days).

Adrenal masses were found on the right side in 23 (54.8%) of 42 cases, on the left side in 13 (31%), and bilaterally in 6 (14.2%). Of a total of 48 adrenal masses, 38 (79.2%) were cystic, 7 (14.6%) were semisolid, 3 (6.2%) were solid, and none of them had calcification at the time of initial diagnosis. Only one patient developed calcification detected by US during the resolution period. Demographic properties and clinical findings of the cases are summarized in Table 1.

TABLE 1: Demographic properties and clinical findings of the cases with neonatal adrenal masses.

	Number (n)	Percent (%)
Sex		
Male	18	42.9
Female	24	57.1
Delivery		
NSVD	35	83.3
C/S	7	16.7
Gestational week		
36-≤38 week	23	54.7
38-≤40 week	17	40.5
>40 week	2	4.8
Birth weight		
2,800 g-≤3,000 g	2	4.8
3,000 g-≤3,500 g	11	26.2
3,500 g-≤4,000 g	19	45.2
>4,000 g	10	23.8
Antenatal diagnosis		
Yes	7	16.7
No	35	83.3
Side of adrenal mass		
Right	23	54.8
Left	13	31
Bilateral	6	14.2
Characteristic of the mass*		
Cystic	38	79.2
Semisolid	7	14.6
Solid	3	6.2

*42 patient had 48 adrenal mass; C/S: Cesarean section; NSVD: Normal spontaneous vaginal delivery.

In the first US, the mean mass size was 34x23 mm (60-6x50-6) and the mean mass volume was 12 mL (0.12-87). The mean mass size was 31x19 mm (52-8x46-5) and the mean mass volume was 8 mL (0.2-58) in the third month US of the patients who were followed up monthly. Although blood flow is not seen in most Doppler USGs, minimal flow has also been reported for same mass in monthly controls.

Vanil mandelic acid level, a urinary tumor marker, was normal in all patients. The mean ferritin level was 425 ng/mL (4-1,520) at the beginning and 216 ng/mL (44-598) at the third month follow-up. Since 38 of 42 patients with a mean hemoglobin value of 15.9±3.25 g/dL (9.1-21.5) in their first hemogram were newborns (1-19 days), 6 (14.3%) patients with a hemoglobin value below 12 g/dL were considered anemic.

The mean initial arterial blood pressure measured during hospitalization for postnatal follow-up of our patients was 77.6/44.4 mmHg (70/36-99/54) and was compatible with their age.

In the monthly outpatient follow-ups, pyeloplasty was performed due to left ureteropelvic junction obstruction in one of the three cases whose lesion size was greater than 16 mL at the age of 5 months. The histopathologies of the other 2 patients who underwent surrenal mass excision at 15 days and 3 months of age were reported as adrenal pseudocyst and benign cystic structures.

DISCUSSION

Adrenal hemorrhage is a relatively rare, variable and nonspecific disease that can cause acute adrenal crisis, shock and death if not recognized early and treated appropriately.[4,5] Vaginal delivery, macrosomia and fetal acidemia are defined as the most important risk factors for adrenal hemorrhage in the newborn.[6] Clavicle fracture in two of our patients and hematoma in the perineum in one of our patients are also evidence of a difficult birth history as a clinical finding.

Neonatal adrenal hemorrhage (NAH) is most common in term babies born vaginally and mostly affects males.[1,7] In this study, NAH was observed more frequently in term babies born vaginally, in line with the literature. On the contrary, our female cases were more common with a rate of 57%.

Adrenal bleeding usually occurs in the right adrenal gland.[1,8] Since the blood flow to the right adrenal gland is directly drained into the inferior vena cava, it is more frequently affected by changes in venous pressure and can be easily damaged by compression between the liver and the vertebrae.[9] Adrenal mass/bleeding was observed in the right adrenal gland in 54% of our cases.

Clinical manifestations of NAH are variable or even absent in most of them. Jaundice, signs of ischemia, palpable abdominal mass and anemia may be detected.[1,7,10,11] Neonatal jaundice, which is caused

by the breakdown of red blood cells, is the most common presentation.[7] Adrenal insufficiency rarely occurs, usually in the first postnatal week. Jaundice requiring phototherapy was present in 45% of the cases in this study, and anemia was detected in 16%. Hypoglycemia, which can be considered as a sign of adrenal insufficiency, developed in only 4.8% of our cases and glucocorticoid treatment was administered.

Due to the possibility of neuroblastoma, urinary catecholamine metabolites are measured in the presence of a mass detected in the adrenal region. However, urinary catecholamine metabolites are often not elevated preoperatively in infants with congenital cystic neuroblastoma, so a negative urine catecholamine test can not exclude the possibility of neuroblastoma. In this study, tumor markers were evaluated in all cases.[12] Consistent with the literature, urinary vanil mandelic acid level was found to be normal in all patients, so it was not possible to exclude neuroblastoma according to urinary vanil mandelic acid level.

NAH is usually self-limited with resolution and complete regression of lesions from day 20 to day 165 of life.[13] The increasing use of perinatal US has led to an increasing number of detection of adrenal masses in neonates. In addition, US is the method of choice for both initial screening and follow-up evaluation for newborns, as it is portable, rapid, sensitive, non-invasive and does not contain ionizing radiation.[1] US/Doppler US was preferred for both initial screening and follow-up evaluation in all patients in the study. With serial US/Doppler US, it is possible to demonstrate resolution of adrenal hemorrhage, but persistence, enlargement or change in nature of the mass may indicate neuroblastoma or another pathology.[7] Sometimes a complex situation may occur due to the combination of necrotic tissue, blood clot, calcification and cyst. Calcification can be seen after the resolution of the hemorrhage, 1-2 weeks after the onset. Presence of calcification on initial imaging may be an indication for neuroblastoma. With this in mind, the usual follow-up should be 90 days for resolution of adrenal hemorrhages and neuroblastoma should be suspected if the mass does not shrink after 3 months.[1] In this study, the mean mass size was calculated as 34x23 mm (60-6x50-6) and the mean mass volume was 12 mL (0.12-87) at the first US. The mean mass size was 31x19 mm (52-8x46-5) and the mean mass volume was 8 mL (0.2-58) in the 3rd month US of the patients who were followed up monthly. Demonstrating the shrinkage and resolution of the masses by US follow-up suggested that they were mostly adrenal hematomas.

Arterial blood pressure measurement of the patient is important in the follow-up of surrenal hemorrhage or neuroblastoma. While hypertension may occur due to mass compression, hypotension may occur due to adrenal insufficiency.[7] Although hypertension is expected mostly in neuroblastoma cases, hypertension may be seen secondary to pushing or compression of renal arteries and veins in large surrenal hemorrhages.[7,14] The mean blood pressure of our patients at the time of hospitalization was 77.6/44.4 mmHg (99-54/70-36) and was compatible with their age. Hypotension or hypertension was not observed in any of our cases.

In a prospective study by Nuchtern et al. published in 2012, 87 patients younger than 6 months of age with small adrenal masses (≤16 mL by volume if solid or ≤65 mL if the mass is at least 25% cystic) and without evidence of extension beyond the primary lesion were followed. Serial abdominal ultrasounds and urinary catecholamine levels of the patients were followed over a period of 90 weeks. Patients with a greater than 50% increase in mass volume and urinary catecholamine value or a homo vanillic acid/vanil mandelic acid ratio of more than 2 underwent surgery. In this context, 83 patients were observed. Sixteen babies in the observation arm eventually underwent surgery. Eight patients had International Neuroblastoma Staging System Stage I neuroblastoma, two had higher stage neuroblastoma (IIB and IV-S), two had low-grade adrenocortical neoplasm, two had adrenal hemorrhage and two had extralobar pulmonary sequestration. Following this protocol, 81% of infants avoided resection, so the role of expected observation in this selected population was supported.[15] As the literature confirms, it is important to perform serial US follow-ups by avoiding early surgical approach and maintain a non-invasive attitude. US is the basic diagnostic method and allows monitoring of changes when repeated over

time.[1] In a recent study, the mean age of surgery was 8.2 months (range: 5 days-3 years) in 6 patients diagnosed during the prenatal period. Indicators for surgery were suspected malignancy, an increase in the size during the follow-up period, and an increase in the neuron-specific enolase level. The histopathological diagnosis was neuroblastoma in 4, hematoma in 1, and cyst in 1 patient.[16] In this study, only three cases with a solid lesion size greater than 16 mL were operated during follow-up. While pyeloplasty was performed in one of them due to left ureteropelvic junction obstruction, the histopathologies of the other two cases were reported as benign cystic structures and adrenal pseudocyst.

During our 14-year follow-up period, none of the patients we operated on had pathology compatible with neuroblastoma. Neonatal neuroblastoma occurs in approximately one in 210,000 live births.[17] A significant proportion of such masses are low-risk neuroblastomas. This group of tumors has the potential to regress completely or differentiate into benign ganglioneuromas.[17] In the light of this information, it is not possible to say that there were no regress neuroblastomas among our cases or that all of our cases that we did not undergo surgery had adrenal hemorrhage.

The follow-up protocol of our clinic was created using the "Untreated Follow-up" Protocol for Perinatal Surrrenal Masses TPOG Infant Surrenal Mass Monitoring Protocol (TPOG-İSKİP) 2011 [Perinatal Sürrenal Kitleler İçin "Tedavisiz İzlem" Protokolü TPOG İnfant Sürrenal Kitle İzlem Protokolü (TPOG-İSKİP) 2011] and "TPOG Neuroblastoma 2020 Protocol" (TPOG Nöroblastom 2020 Protokolü).[17,18] Our patients' age were less than 3 month and US of the patients who were followed up monthly. The volume (V) of the mass defined by sonographic examination was calculated as follows.[17] Adrenal masses (≤16 mL by volume if solid or ≤65 mL if the mass is at least 25% cystic) and without evidence of extension beyond the primary lesion were followed. And vanil mandelic acid was studied in spot urine as a tumor marker. The most striking difference of our study from this protocol is due to the need for anesthesia because the patient had to be immobile during magnetic resonance imaging, magnetic resonance imaging was preferred only in a few of our patients, according to our close follow-up US results.[19]

CONCLUSION

It can be difficult to make a differential diagnosis between neonatal neuroblastoma and adrenal hemorrhage. When a conservative approach is preferred without early surgery, follow-up with serial sonographic examination and laboratory findings is the most reliable method.

Source of Finance

During this study, no financial or spiritual support was received neither from any pharmaceutical company that has a direct connection with the research subject, nor from a company that provides or produces medical instruments and materials which may negatively affect the evaluation process of this study.

Conflict of Interest

No conflicts of interest between the authors and / or family members of the scientific and medical committee members or members of the potential conflicts of interest, counseling, expertise, working conditions, share holding and similar situations in any firm.

Authorship Contributions

Idea/Concept: *Olga Devrim Ayvaz;* ***Design:*** *Olga Devrim Ayvaz, Ayşenur Celayir;* ***Control/Supervision:*** *Olga Devrim Ayvaz, Ayşenur Celayir;* ***Data Collection and/or Processing:*** *Olga Devrim Ayvaz, Sabri Cansaran, Cengiz Gül;* ***Analysis and/or Interpretation:*** *Olga Devrim Ayvaz, Sabri Cansaran, Ayşenur Celayir;* ***Literature Review:*** *Olga Devrim Ayvaz, Sabri Cansaran, Cengiz Gül;* ***Writing the Article:*** *Olga Devrim Ayvaz, Sabri Cansaran;* ***Critical Review:*** *Olga Devrim Ayvaz, Sabri Cansaran, Ayşenur Celayir;* ***References and Fundings:*** *Olga Devrim Ayvaz, Sabri Cansaran, Cengiz Gül, Ayşenur Celayir;* ***Materials:*** *Olga Devrim Ayvaz, Ayşenur Celayir.*

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