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Differential Diagnosis and Management In Neonatal Mass Lesions: Ten Years Experience

Yenidoğan Dönemindeki Kitlesel Lezyonlarda Ayırıcı Tanı ve Yönetim: On Yıllık Tek Merkez Deneyimi

ABSTRACT

Objective:
Neonatal tumors are rare and there is no standard approach to these diseases. The aim of this study is to analyze the incidence, clinical features and management of these exceptional tumors which were followed-up at our center.

Material and Methods:
We assessed all babies with solid masses admitted to our hospital between December 2007 and December 2018, retrospectively. The age, sex distribution, birth weight and gestational age, type of lesion, management and outcome were studied.

Results:
Of total; there were 62 cases over 10 years in which the most common solid neonatal tumor was germ cell tumor (30.6%). Thirty eight (61.3%) of all cases were malignant tumors. Forty two lesions (67.8%) were located in the abdomen. The majority of cases (48.3%) underwent only surgery for treatment strategy. Twelve cases (19.4%) were preterm. Forty percent of the lesions were detected in the prenatal period.

Conclusion:
Despite limited management experience for newborn tumors, thanks to renovations in prenatal diagnostic methods and sufficient perinatal care, survival can be improved in specialized multidisciplinary centers. In addition to this, it would be beneficial for centers following these patients to share their experiences.

Key Words:
Antenatal diagnosis, Neonatal tumors, Premature, Survival, Treatment

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ÖZ

Amaç:

Yenidoğan tümörleri nadirdir ve bu hastalıklara standart bir yaklaşım bulunmamaktadır. Bu çalışmanın amacı, merkezimizde izlediğimiz bu istisnai tümörlerin insidansını, klinik özelliklerini ve yönetimini analiz etmektir.

Gereç ve Yöntemler:

Hastanemizde Aralık 2007 ile Aralık 2018 tarihleri arasında takip ettiğimiz solid kitlesi olan bebekleri retrospektif olarak değerlendirdik. Yaş, cinsiyet dağılımı, doğum ağırlığı ve gebelik yaşı, lezyon tipi, vakaların yönetimi ve sonuçlar incelendi.

Bulgular:

On yıllık süre içinde toplam 62 vaka tespit edilmiş olup en sık görülen solid neonatal tümör germ hücreli tümör idi (%30,6). Tüm vakaların 38'i (%61,3) malign tümörlerdi. Kırk iki lezyon (%67,8) karında yerleşmekteydi. Olguların büyük çoğunluğuna (%48,3) tedavi olarak sadece cerrahi uygulandı. Olguların 12'si (%19,4) preterm idi. Lezyonların %40,3'ü prenatal dönemde tespit edildi.

Sonuç:

Tüm dünyada olduğu gibi ülkemizde de yenidoğan tümörleri için sınırlı yönetim deneyimine rağmen, doğum öncesi tanı yöntemlerindeki yenilikler ve yeterli perinatal bakım sayesinde, uzmanlaşmış multidisipliner merkezlerde hastaların sağkalımı artırılabilir. Ayrıca bu hastaları takip eden merkezlerin deneyimlerini sunması faydalı olacaktır.

Anahtar Kelimeler:

Antenatal tanı, Neonatal kitleler, Prematür, Sağkalım, Tedavi

INTRODUCTION

The neonatal period has unique features in childhood. An enormous growth during the prenatal phase requires rapid cellular proliferation and differentiation. As a consequence of this process, certain uncontrolled cellular growth can lead to hematological malignancies and solid tumors. Furthermore, pathological lesions can display different clinical behavior than toddlers and older children in this period (1). This feature has always been a diagnostic challenge for pediatricians. Besides, rare tumor incidence in this period of life (a prevalence of 1 case in 12.500-27.500 live births) gives rise to less clinical experience in medical literature and clinicians have to use personalized methods for most cases in their daily practice (2).

Tumoral diseases, which are the leading causes of death in childhood, constitute approximately 6.26 death per million live births in the neonatal period (3). These tumors, which originate from immature cells, may not be well-responded to treatments. Other accompanying problems (prematurity, congenital anomalies, respiratory dysfunction, etc.) and poor responsiveness to treatments are defined as the most important causes of death (4). There is a considerable requirement for more studies on follow-up and treatment approaches. For this purpose, we present our experience and clinical data about neonates diagnosed and referred to our hospital in this study.

MATERIAL and METHODS

The data of neonates who were diagnosed between December 2007- December 2018, with mass lesions and their follow-up were analyzed retrospectively. The variables of the study were age, sex, delivery way, birth weight, gestational age, time of prenatal diagnosis, primary tumor site, type of tumor, clinical and histological features, management and status at last follow-up. Babies born before 37 gestational weeks were considered preterm, while those born 37 gestational weeks and above were considered full-term. Patients with infantile cutaneous haemangiomas were excluded.

All procedures performed in studies involving human participants were in accordance with the ethical standards of the institutional and/or national research committee and with the 1964 Helsinki declaration (as revised in 2013) and its later amendments or comparable ethical standards. Informed consent was obtained from all individual participants' legal guardians or parents included in the study. This study was approved by Baskent University Medical and Health Sciences Research Board (Project no: KA21/359) and supported by Baskent University Research Fund.

Statistical analysis

Statistical analysis were carried out using the SPSS 22.0. Categorical measurements were summarized as frequency and percentages, and continuous measurements as mean, minimum-maximum, and median.

RESULTS

Of 62 patients diagnosed with a neonatal mass, 38 were (61.3%) female individuals in this study. Fifty patients (80.6%) were full-term and the median birth weight was 3432 gr (min: 1600 gr, max: 5900 gr). Twelve patients (19.4%) were preterm and the median birth weight was 2920 gr (min: 1800 gr, max: 3840 gr).

Twenty five cases (40.3%) were diagnosed prenatally through screening by ultrasonography between 14 and 37 gestational weeks. In these cases, eighteen lesions were located in the abdominal region and most of them were germ cell tumors (n=10, 40%). Eight (32%) of 25 cases were born prematurely. The median birth weight of these cases was 2786 gr and all of them were delivered by cesarean section.

For all cases, according to the primary tumor site; the abdominal region was the most common site (n=42, 67.7%), followed by head-neck (n=11, 17.7%) and chest (n=6, 9.7%). While the primary tumor region was the abdomen

in all patients with neuroblastoma, in terms of germ cell tumors; fourteen of them (73.6%) were located in the abdomen (Table I). The histopathological confirmation was made in 46 cases. Forty of them underwent surgery, and 6 lesions were documented with tru-cut biopsy. Other cases were evaluated with their clinical aspects and radiologic features (Table I).

In this study, germ cell tumors were the most prevalent tumors (n=19); the primary tumor localization was the sacrococcygeal region in 13 (68.4%), head and neck in 4 (21%), chest in 1 (5.2%) and adrenal gland in 1 (5.3%). In 16 of 19 patients; tumors were resected totally. Histopathological examination showed 9 mature cystic teratomas, 9 immature teratomas and 1 malign germ cell tumor. Chemotherapy was administered to two patients because of relapsed disease or progressive disease. First one had an immature teratoma in the coccyx region in whom disease relapse had been occurred at 18 months and she died at 32 months after the initial diagnosis. The other patient with a tumor in the orbita underwent surgery and chemotherapy because of transforming into a malignant glial tumor, but she died of resistant disease at 32 months from diagnosis (Figure 1c). Seventeen of 19 patients with germ cell tumors are disease-free in a median follow-up of 5 years from diagnosis.

Fourteen patients were diagnosed with surrenal mass which was the second-most common solid lesion in our study. Four of them were diagnosed antenatally. Eight patients who were thought to have neuroblastoma with radiological and clinical findings were followed closely because of the possibility of spontaneous regression. One of these cases had a diagnosis of Trisomy 18 and died 4 months after diagnosis from complications associated with Trisomy 18. The histopathological diagnosis was neuroblastoma in five patients. One patient underwent surgery in a local hospital and the course was uneventful during the follow-up. Adrenalectomy was performed in one patient who showed some signs of the opsoclonus-myoclonus-ataxia syndrome (head titubation and restlessness) in the follow-up. Then she was applied IVIG and corticosteroids for four months. She is still under follow-up for 40 months without symptoms. Two patients who were followed up firstly, received chemotherapy and were treated with surgery due to progression to Stage IV-S. Of the whole surrenal masses, only one patient had been diagnosed with mature cystic teratoma after surgery.

Other rarely diagnosed malignant tumors were malignant mesenchymoma (n=2), hepatoblastoma (n=2), renal clear cell sarcoma (n=1) and spinal glial tumor (n=1). In one of the patients with malignant mesenchymoma the primary tumor was in the head base and was not responsive to neither chemotherapy nor surgery (Figure 1b). He died of progressive disease. The other patient with an abdominal tumor responded to chemotherapy and surgery at first, but late disease recurrence was detected after 45 months of the first diagnosis. The family refused further intervention and treatment. One of two patients with hepatoblastoma was diagnosed during the prenatal period (Figure 1e, f). They were treated with surgical excision after chemotherapy. They are still under follow-up and disease-free for 47 and 136 months. The patient with renal clear cell sarcoma died of widespread metastatic and uncontrolled disease in the first month of diagnosis. The patient with a malignant spinal glial tumor had widespread leptomeningeal metastasis and despite intensive chemotherapy, she died of respiratory insufficiency.

In the neonatal period, the most common vascular tumors were haemangiomas (n=7) and lymphangiomas (n=4) (Table I). Oral prednisolone and propranolol were administered to 6 patients who had been diagnosed with rapidly involuting capillary haemangioendothelioma (RICH) (Figure 1d). Five of these lesions regressed with these treatments. Only one patient died due to coagulopathy as a consequence of Kasabach-Merritt syndrome. The lesion was located in the leg and had no response to treatment with propranolol, oral and intravenous corticosteroids, chemotherapy and radiation therapy. This is the only patient we had to apply radiotherapy in the neonatal period. Lymphangiomas (n=4) were the second-most common vascular lesions and they were all located in the neck region. Two had macrocystic pattern and shrank after sclerosing therapy. The microcystic lymphangiomas (n=2) were treated with surgery only. But one of the patients with microcystic lymphangioma needed a tracheostomy to provide intact respiration. He died due to respiratory issues after discharge.

Other rare lesions which exhibit benign features were mesenchymal hamartoma, congenital mesoblastic nephroma, leiomyoma, ovarian cysts and lipoblastoma. All of these benign masses were surgically removed and they are all disease-free during this review. The patient with plexiform neurofibroma in the retroorbital region had been observed only for 62 months. Patients with cardiac rhabdomyoma and cystic adenoid malformation had been diagnosed in the antenatal period and they were followed up for 41 months and 7 months respectively without surgery.

Table I. Clinical features of the mass lesions in newborns

		Diagnosis			Adjuvant Treatment		Outcome
	N	Surgery	Biopsy	Clinical*	Chemotherapy	Others	
ABDOMEN	**42**						
Sacrococcyx	13						
Germ cell tumor	13	13	-	-	-	-	12 Al, 1 Ex
Surrenal gland	14						
Surrenal mass	8	-	-	8	-	-	2 Lo, 5 Al, 1 Ex
Neuroblastoma	5	5	-	-	2	1	5 Al
Germ cell tumor	1	1	-	-	-	-	1 Al
Liver	5						
Haemangioma	3	-	2	1	-	3	3 Al
Hepatoblastoma	2	2	-	-	2	-	2 Al
Ovarian	3						
Ovarian cyst	3	3	-	-	-	-	3 Al
Kidney	2						
Clear cell sarcoma	1	-	1	-	-	-	1 Ex
Mesoblastic nephroma	1	1	-	-	-	-	1 Al
Peritoneal	3						
Malign mesenchymal tumor	1	1	-	-	1	-	1 Al
Hamartoma	2	2	-	-	-	-	2 Al
Intestine	1						
Leiomyoma	1	1	-	-	-	-	1 Al
Vulva	1						
Lipoblastoma	1	1	-	-	-	-	1 Al
HEAD-NECK	**11**						
Neck	9						
Lymphangioma	4	2	-	2	-	2	2 Al, 1 Lo, 1 Ex
Germ cell tumor	3	3	-	-	-	-	3 Al
Malign mesenchymal tumor	1	1	-	-	1	-	1 Ex
Spinal glial tumor	1	-	-	1	1	-	1 Ex
Eye	1						
Germ cell tumor	1	1	-	-	1	-	1 Ex
Retroorbital region	1						
Plexiform neurofibroma	1	-	1	-	-	-	1 Lo
CHEST	**6**						
Lung	3						
Cystic adenomatoid malformation	1	-	-	1	-	-	1 Al
Hamartoma	2	2	-	-	-	-	2 Al
Mediastinum	2						
Germ cell tumor	1	1	-	-	1	-	1 Al
Haemangioma	1	-	-	1	-	1	1 Al
Heart	1						
Rhabdomyoma	1	-	-	1	-	-	1 Al
EXTREMITY	**3**						
Skin	3						
Congenital Haemangioma (RICH)	3	-	2	1	1	3	2 Al, 1 Ex

*Al: Alive; Ex: Exitus; Lo:Lost to follow-up; RICH: rapidly involuting congenital haemangioma; * Radiology in majori*

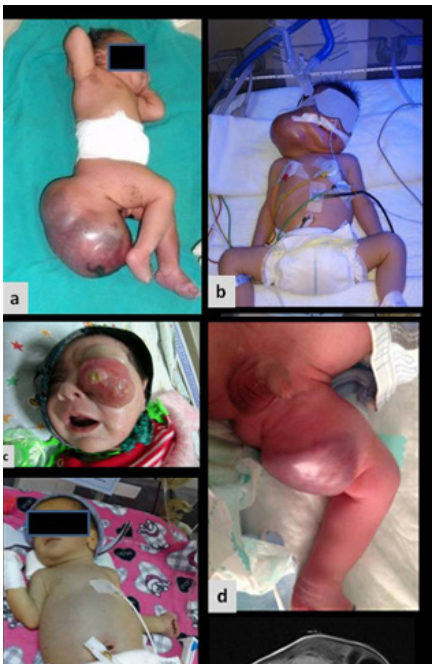

Figure 1. A sacrococcygeal teratoma in a newborn; the birth weight had been changed by the mass (a); cervical malignant mesenchymal tumor in a neonate (b); malign germ cell tumor in a neonate in the eye (c); rapidly involuting congenital haemangioma in femoral region (d); hepatoblastoma in another patient with abdominal mass and MRI appearance (e,f)

DISCUSSION

Neonatal tumors are rare and because of mimicking embryonal cells their clinical behavior cannot be predictable. Therefore, their managements are not easy. Centers that follow these patients generally present their limited experiences to the literature. In a way that supports it, in several studies neuroblastoma and germ cell tumors are the most common tumors with variable frequency in the neonatal period (2, 5). According to Desandes and colleagues' study, the most common neonatal malign tumors were neuroblastoma and germ cell tumors respectively (47% vs 28.8%) (5). In our study, germ cell tumors were the most prevalent tumors. This difference reflects the fact that mature teratomas were included in the study group.

Nowadays courtesy of advances in fetal ultrasonography, prenatal diagnosis of many tumors can be made easily. In this study, 40.3% of the cases were diagnosed in the prenatal period. Thirty two percent of them were preterm. In terms of mean birth weight of preterm babies diagnosed antenatally were similar to all of the full-term babies (2200-3750 gr, mean: 2786 gr). It is probably due to the impact of tumor size on the patient's weight (Figure 1a). There is also still limited data about the birth weight of premature babies with a solid tumor in the literature, likewise in Raciborska and colleagues' study, sacrococcygeal teratomas were associated with premature delivery (6). Besides that, all these babies with sacrococcygeal teratomas were delivered prematurely via elective cesarean section (7, 8). We assume that obstetricians followed prenatally consid-

ered the time of birth due to enlargement of the mass and complications of normal the way of delivery. Nevertheless these babies can be delivered via normal vaginal way taking into account whole clinical aspects. There are some valuable indicators like polyhydramnios, placentomegaly, cardiac failure and hydrops fetalis which are associated with adverse outcomes. So they are important to schedule time for delivery as referring to some studies (9-11). In addition, it is known that low birth weight and prematurity are strongly associated with hepatoblastoma (12). However, the patients with hepatoblastoma in our study were full-term and normal birth weight (40 gestational week and 3350 gr vs 38 gestational week and 2700 gr).
Neonatal tumors may locate in any part of the body. In our study, the masses resided mostly in the abdominal region (67.7%) (Table I). If any tumoral mass is detected in a newborn baby's abdomen, neuroblastoma is the tumor that should be researched first. After that, other uncommon causes could be investigated. In addition to this, orbital germ cell tumor, which is one of the extraordinary cases in our study, is really rare. So more common intraocular neoplasms must be excluded before the last decision (e.g. retinoblastoma) (13).

Although some tumors may need surgical intervention or chemotherapy, some of the others can regress spontaneously. In our study 21% of cases were followed without any treatment approach. Of all 48.3% underwent only surgery, 1.6% received only chemotherapy, 13% were treated with both chemotherapy and surgery. In 16.1% of cases were applied both drugs other than chemotherapy (i.e. propranolol) and surgery. As in many studies in the literature, surgery is the fundamental treatment modality for newborn solid tumors (5, 14, 15). Chemotherapy is usually used only in selected cases. One patient who was diagnosed with spinal glial tumor had been only treated with chemotherapy in our study group. One patient had been applied radiotherapy and non-chemotherapeutical drugs. Because of the long-term consequences of radiotherapy, this modality is usually avoided in the neonatal period, but we had to apply radiotherapy to a patient with Kasabach Merritt syndrome considering all adverse effects. Treatment options should be carefully reviewed, considering the location of the tumor, histological type, life-threatening symptoms and laboratory findings. Besides it is vital to follow adrenal masses which have unique nature for only infants, without any intervention carefully as well as morbidity and mortality. However, it should be kept in mind that it is difficult to distinguish neuroblastoma located in the adrenal gland from adrenal hemorrhage due to difficult delivery in the neonatal period. Because of this, suspicious cases should be evaluated with further investigations (16-19).

Study Limitations

Our study has some limitations due to the limited number of patients and tumors' rarity like other similar studies. In addition, we could not diagnose all patients histopathologically. Besides, we think that we have contributed to the literature by giving the disease and follow-up results of our patients who especially require chemotherapy and radiotherapy, which can be applied to a small number of patients in the neonatal period.

CONCLUSION

To summarize, surgery and chemotherapy (more rarely) are the mainstay therapeutical approach for solid tumors in the neonatal period, nonetheless chemotherapeutical agents should be given with dose adjustments cautiously for patients who are already immature for renal and hepatic functions in this period of life. Clinicians should take care of optimal therapy with minimal toxicity. Although almost all of the cancers' prognosis for the other childhood tumors improved, neonatal malignancies have still lower survival. It may be associated with the rarity of tumors in this period of life and also not being achieved adequate experiences in management. Courtesy of advances in prenatal diagnostic methods and sufficient perinatal care, survival can be improved in highly specialized multidisciplinary centers.

Ethics Committee Approval:
This study was approved by Baskent University Medical and Health Sciences Research Board (Project no: KA21/359) and supported by Baskent University Research Fund.

Conflict of Interest:
The authors declare that they have no conflict of intere

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Author Contribution:
E.H.A. designed and performed the research, wrote the paper. A.E. designed the research and analyzed the data. S.S.E. performed the research. B.Ç. performed the research and analyzed data. Ş.K.D. performed the research. B.H. performed the research and analyzed data. N.Y. performed the research and wrote the paper.

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