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Epidemiology of Neonatal Cancer and its Correlation with Different Factors

Maliheh Kadivar, Mahsa Asadabadi*

Department of Pediatrics, Children's Medical Center, School of Medicine, Tehran University of Medical Sciences, Tehran, Iran

ABSTRACT

***Background*:** Tumors are among the main causes of neonatal intensive care unit (NICU) admission. We aimed to determine the frequency distributions and presentations of tumors in newborns admitted to the NICU of a children's medical center.

***Methods*:** In this observational cross-sectional study, we reviewed medical records of 53 neonates admitted to the NICU of a children's medical center during 2004-2015. The demographic characteristics, maternal history, ultrasound findings during pregnancy, and family history of cancer were considered along with clinical presentations. To determine the tumor type, imaging and pathological reports were collected from the medical records. Tumors were classified according to the International Classification for Childhood Cancer criteria (ICCC). The gathered data were analyzed using SPSS, version 19.

***Results*:** The mean maternal age and gestational age of the newborns were 24.4±4.9 years and 37.4±2.01 weeks, respectively. Twenty-nine (54.7%) subjects were female, and 12 (22.6%) infants were preterm. The parents of 19 infants (35.8%) had consunguity, but positive family history was not identified in any of the newborns. Thirteen (24.5%) patients had congenital anomalies. Neonatal cancer was diagnosed through prenatal ultrasonography in 16 (30.2%) infants, and 17 (32%) cases had malignant tumors. Among these newborns, 37 (69.8%) underwent surgery, 13 (24.5%) patients received medications, 1 (1.9%) patient had chemotherapy, and 2 (3.8%) patients received both surgery and chemotherapy. Ten (18.9%) subjects died at the end of the study. Furthermore, 18 (34%) tumors were mature teratomas, 11 (20.8%) cases were hemangiomas, 7 (13.2%) were neuroblastomas, and 6 (11.3%) cases were lymphangiomas.

Conclusion: According to the results of this study, teratoma is the most common tumor among the newborns admitted to NICUs, and head and neck were the most common locations. In addition, neuroblastoma was associated with the highest mortality rate in this study.

Keywords: Malignancy, Neonatal intensive care unit, Newborn, Tumor

Introduction

Neonatal tumors are uncommon and the annual rate of different kinds of neonatal tumors is estimated to be 1 out of 12000-27500 cases (1). In fact, only 2% of childhood tumors are observed in infancy (2). Most tumors specifically present in infancy, and if older children get involved with the disease, they show different manifestations. Lack of awareness regarding neonatal tumors is one of the possible reasons for the late diagnosis and appropriate treatment of the disease. Some benign tumors might be considered invasive at first, and some others, which are apparently malignant, can be deadly if not removed (3).

Today, fetal survey techniques are applied before birth to treat fetal tumors (2). Approximately, 40% of malignant neonatal tumors are recognized during the first hour and the rest during the first week after birth. However, 17% of the mentioned cases are only diagnosed after autopsy (3-5). Despite the fact that the fetus is exposed to several chemical, physical, and bacterial factors in the mother's uterus and this can raise the risk of neonatal malignancies, it seems that the distorting factors that put a limit on the studies performed on adults cancers, play an unimportant role on neonatal malignancies(6). Small mutations and defects in heterogenecity and genomic imprinting are those genetic mechanisms that cause cancer through affecting the genes that regulate cell cycle, apoptosis, and cell evolution

* *Corresponding author*: Mahsa Asadabadi, Department of Pediatrics, Children's Medical Center, School of Medicine, Tehran University of Medical Sciences, Tehran, Iran. Email: mah.asadabadi@gmail.com

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(7, 8). Benign tumors are quite common in infancy and many of them usually go undiagnosed. Hemangioma is only diagnosed in 6-25% of infants after birth. Melanocytic nevi are seen in 3% of Caucasian children, and 16% of them occur in other races. On the contrary, congenital malignant melanoma is rare in infants (2). Teratoma is the most common infantile tumor; however, the most common malignant tumors in this group of patients are neuroblastoma, leukemia, renal tumor, mesenchymal tumor, and neural tissues (1, 9). Although palpating the lump is the first method of disease diagnosis in many cases, roughly 34% of them are recognized by metastasis or accidentally (10).

According to the former studies, various factors are at paly in the incidence of cancer including geographical area and race; furthermore, the incidence of cancer is different among diverse population groups (11, 12). Nevertheless, there is a scarcity of comprehensive studies in Iran on neonatal tumors. We attempted to estimate the frequency distributions of different tumors and the effective factors in infants admitted to the neonatal intensive care unit (NICU) of a tertiary referral center since the beginning of 2002 through the end of 2016.

Methods

This cross-sectional study was performed with a case-series design. The medical records of all the infants diagnosed with tumor, who were admitted to the NICU of a tertiary care center during 2004-2015 were reviewed. After considering the records, we studied the infants presenting with any kind of tumor based on the ethical values and after obtaining approval of the Ethics Committee of Tehran University of Medical Sciences.

In addition to the demographic characteristics such as age, gender, and gestational age, mother's status in terms of having sonography during pregnancy, history of cancer, or any contact with physical, chemical and microbial factors was checked. Clinical presentations were considered from different aspects based on mass type.

To detect the tumor type, the imaging and pathological reports were collected from the infants' medical records. Those cases whose pathology assessment results showed tumor formation based on genetic disorders were taken under consideration according to the cytogenetics.

A wide range of tumors are classified in accordance with the International Classification for Childhood Cancer criteria (ICCC). Therefore, different kinds of tumors were analyzed in 12 main groups, each of them were put under a subgroup accordingly. The gathered data from 53 cases were analyzed using SPSS, version 19. quantitative data was reported as standard deviation± mean and qualitative data in the form of absolute frequency and relative one. The rest of findings were demonstrated as tables and appropriate diagrams. P-value less than 0.05 was considered statistically significant.

Results

Initially, 66 infants diagnosed with tumor were selected, 13 of whom were excluded due to not having medical records or lack of access to them. The mean maternal age was 24.4±4.9 years (age range: 18-41 years). The mean age of pregnancy was 37.4±2.1 weeks (range: 28-40 weeks). Twenty-nine (54.7%) of the infants were female, and 41 (77.4%) of the neonates were born term. All the mothers had conceived naturally. Furthermore, 19 (35.8%) infants had adopted parents, and no positive family history was found in the infants. Seven (13.2%) infants had congenital defects. Additionally, 16 (30.2%) children had perinatal tumor diagnosis by ultrasound during pregnancy.

In general, 17 (32%) patients suffered from malignant tumors and 36 (68%) of them were diagnosed with benign tumors. The mean time elapsed till tumor presentation after birth was 2.1±2.3 days (range: 1-15 days). Furthermore, the infants' mean age on admission was 2.3±2.1 days (range: 1-48 days), and the mean duration of NICU stay was 14.2±8.5 days (range: 3-38 days). Overall, 37 (69.8%) infants underwent surgery, 13 (34.5%) pharmacotherapy, and 1 (1.9%) chemotherapy. Moreover, two (3.8%) patients received both surgery and chemotherapy. During stay in this ward, 43 (81.1%) of the infants survived, while 10 (18.9%) of them died.

As can be observed in Table 1, head and neck were the most frequent (26.4%) tumor locations, followed by the abdomen (18.9%), skin (17%), and sacrum (17%). Additionally, as presented in Table 2, the most common types of tumors were teratoma (34%), hemangioma (20.8%), neuroblastoma (13.2%), and lymphangioma (11.3%). Teratoma (over 50%) and neuroblastoma (41.2%) were respectively the most common benign and malignant tumors. Twenty (37.7%) neonates presented serious symptoms before treatment, which mostly included bleeding (5.7%) and hydronephrosis (5.7%). The other complications were paresis (3.8%), metastasis

Table 1. The frequency of tumor locations

Presentation location	Frequency	Percentile
Neck and head	14	26.4%
Abdomen	10	18.9%
Cutaneous hemangioma	9	17.0%
The sacrum	9	17.0%
Mediastinum	4	7.5%
Lumbosacral	5	9.4%
Cardiac	1	1.9%
Axillary	1	1.9%
Total	53	100.0%

Table 2. The frequency of different tumor pathologies

Pathology type	Frequency	Percentile
Mature teratoma	18	34.0%
Hemangioma	11	20.8%
Neuroblastoma	7	13.2%
Lymphangiomas	6	11.3%
Immature teratoma	5	9.4%
Rhabdomyoma	2	3.8%
Rhabdomyosarcoma	1	1.9%
Mesenchymal hamartoma	1	1.9%
Choriocarcinoma	1	1.9%
Fibrosarcoma	1	1.9%
Total	53	100.0%

(3.8%), apnea (3.8%), and heart failure (3.8%; Table 3). Besides, 10 (18.9%) patients suffered from adverse side effects after the intervention, 4 (5.7%) had relapse, 3 (5.7%) developed urinary tract infection, and 3 (5.7%) suffered from seizure.

As noted in Table 4, there were no differences

Table 3. The frequency of different kinds of disease complications before treatment

Complications	Frequency	Percentile
Hydronephrosis	3	5.7%
Bleeding	3	5.7%
Paresis	2	3.8%
Metastasis	2	3.8%
Apnea	2	3.8%
Heart failure	2	3.8%
Anemia	1	1.9%
Convulsion	1	1.9%
Intraventricular Hemorrhage	1	1.9%
Cellulitis	1	1.9%
Ptosis	1	1.9%
Respiratory distress	1	1.9%
No complications	33	62.3%
Total	53	100.0%

Table 4. The comparison of different factors in the understudy infants separated by tumor identity

		Benign (n=36)	Malignant (n=17)	P-value
Gender	Male	14(38.9%)	10(58.8%)	0.174
	Female	22(61.1%)	7(41.2%)	
Gestational age	Term	28(77.8%)	13(76.5%)	0.915
	Immature	8(22.2%)	4(23.5%)	
Adopted parents	Yes	15(41.7%)	4(23.5%)	0.199
	No	21(58.3%)	13(76.5%)	
Prenatal diagnosis	Positive	10(27.8%)	6(35.3%)	0.578
	Negative	26(72.2%)	11(64.7%)	
Congenital defects	yes	9(25.0%)	4(23.5%)	0.908
	No	27(75.0%)	13(76.5%)	
Living status	Normal	31(86.1%)	12(70.6%)	0.178
	Died	5(13.9%)	5(29.4%)	
Alpha-fetoprotein	Normal	30(83.3%)	10(58.8%)	0.053
	Elevated	6(16.7%)	7(41.2%)	
Beta-human chorionic gonadotropin	Normal	34(94.4%)	15(88.2%)	0.424
	Elevated	2(5.6%)	2(11.8%)	
Vanillylmandelic acid	Normal	35(97.2%)	12(70.6%)	0.004
	Elevated	1(2.8%)	5(29.4%)	

between the infants with malignant and benign tumors in terms of age, gestational age, consanguinity, birth defects, living status, alpha-fetoprotein, and the level of beta-human chorionic gonadotropin (P>0.05), but the level of vanillylmandelic acid in the infants with malignant tumors was significantly higher than others (P=0.004). Tumor type did not show any significant association with gestational age and duration of NICU stay (P>0.05).

Discussion

Tumors are rare in infants, and the number of infants and young children affected with tumors is significantly less than older children in both specific and general tumors (13). Perek et al. (14) studied tumors among infants aged under three months, Campbell et al. (5) analyzed neonatal cancer, Halperin et al. (15) investigated different types of neonatal tumors, Moore et al. (1) took epidemiology of neonatal tumors under consideration, Hwan et al. (16) evaluated diagnostic tools and the treatment of central nervous system tumors in infants. Moreover, Ferrari et al. (17) analyzed soft tissue sarcoma in infants. The present study was conducted to analyze the frequency of different types of tumors in infants admitted to an NICU during 2004-2015;

in general, 53 infants suffering from tumors were enrolled.

In our study, 54.7% of the affected infants were female. Similarly, the study by Perek et al. investigated different types of tumors in infants aged under three months, and from 71% of the patients, 48% of them were female. In other similar studies, there were no significant differences between the two genders in terms of tumor development (1, 18, 19). Nevertheless, in a similar study performed by Halperin et al., 70% of the infants affected by neoplasm were females (15). The observed difference may be attributed to the sampling technique and the smaller sample size in this study compared to others.

Although malignant tumors are not common in the neonatal period, 32% of the tumors were malignant in our study. Benign tumors can also function as malignant tumors based on their size and location. The main problem with clinical classification is that malignant histologic appearance in pathology is not always adjusted with clinical tumor behavior (1, 3, 20). Tumors with local invasion to the adjacent tissues might not have metastasis, and tumors that obviously have malignant pathological appearance show unpredictable behaviors. Although screening programs have made it easier to detect many of the immature tumors, patient prognosis has not changed (1). Tumors are most commonly diagnosed through prenatal sonography (18, 19). According to Isaacs et al., the most common primary presentation of the disease was the existence of tumor in prenatal sonography or infant's examination and the second most common presentation was polyhydramnios. In our study, 16 infants (30%) had perinatal tumor diagnosis, of whom 15 had fetal sonography and one of them had oligohydramnios.

In accordance with our findings, the highest frequency of tumor pathology pertained to mature and immature teratomas (43%). Similarly, Perek et al. (14) analyzed 71 patients during 1996-2004, the most common neonatal tumor was germ cell, which comprised 60% of the cases, 52% of which were immature teratomas. Halperin et al. (15) assessed 23 infants affected by neoplasm during 1980-1998, they mentioned that teratoma and germ cell were the most common tumors. Teratoma was reported to be the most abundant neonatal neoplasm affecting one-fourth or one-third of the whole cases (22, 21).

Neonatal tumors are rarely malignant, and the most frequently affected location was the sacrococcygeal area (22, 23). In our study, the most commonly affected site with neoplasm was the sacrococcygeal area. Isaacs et al. (18) carried out a study on 534 fetuses and infants and compared them with older children in terms of clinical and morphological differences of germ cell tumors. They concluded that the number of mature and immature teratomas was almost the same, while the prevalence of mature teratoma in our subjects was considerably higher than immature teratoma. This difference might arise from limited sample size. According to our study, the prevalence rates of hemangioma and teratoma were higher in females than males. Consistent with our findings, in another study, six females and two males were found to have germ cell tumor and teratoma (15).

The second most common tumor type in our study was hemangioma with the rate of 20.8%. The rate of neonatal hemangioma was reported about 1-5% in other studies (24, 25). Besides, low birth weight and female gender were the risk factors for neoplasm among Caucasian infants (25, 26). According to our findings, the prevalence of this tumor in females (31%) was higher in comparison to males (8.3%), while there was no significant difference between term and preterm neonates.

Neuroblastoma with the prevalence rate of 13.2% was the third most common tumor in the current study. Perek et al. (14) showed that neuroblastoma with the rate of 22% was the second most common tumor in this group of patients. However, Campbell et al. (5) conducted a study to assess neonatal malignant tumors among a sample of 102 infants. In that study, neuroblastoma with the rate of 47% was the most frequent type of malignant tumors. Likewise, among malignant tumors in our study, the highest frequency rate belonged to neuroblastoma with the rate of 41%. In the studies by Halperin et al. (15) and Moore et al. (1), neuroblastoma was the second most common tumor.

In the current study, 13.2% of infants had birth defects; in this regard, there was not any significant difference among the infants born to consanguineous parents and others. According to the findings of similar studies, in 15% of cases a relationship was noted between prenatal disorders and types of tumors. Tumors associated with genetic disorders, such as retinoblastoma, are most probably malignant. Furthermore, it seems that some specific cytogenetic disorders are only observed in neonatal tumors (1). In our study, lymphangioma and neuroblastoma had the

highest association with birth defects.

Urine catecholamine level and its metabolites, including vanillylmandelic acid (VMA), can help with neuroblastoma diagnosis in 90% of the cases (27, 28).). In a study, the Serum level of VMA was evaluated in patients affected by Neuroblastoma but its level was increased slightly lower than urine (29). The level of the metabolite rarely elevates, and if an increase is noted in clinical and pathological findings, there is no chance of neuroblastoma (29, 30). In our cases, the level of metabolite in infants affected by malignant tumors, such as neuroblastoma, was significantly higher than that of infants affected by benign ones. Previous studies also demonstrated that having tumor with higher levels of VMA as an index can indicate a weak prognosis (31, 32), which is in line with our findings. The survival rate is considerably lower in patients with increased higher level of VMA compared to others, and consequently, 4 out of 6 patients died.

Additionally, previous studies noted that the level of beta-human chorionic gonadotropin elevates in some of malignancies such as germ cell and choriocarcinoma (29, 32). There was also an increase in the level of alpha-fetoprotein in some tumors like hepatoblastoma and hepatocellular carcinoma (30, 31). However, in our findings, malignant and benign tumors were not significantly different in this regard.

The findings of the present study indicated that 43 (81.1%) patients were alive when they were checked up for the last time. Ten (18.9%) infants had died, five of whom were in the benign neoplasm group and five others belonged to the malignant group. Although the mortality rate in infants affected by malignant neoplasm was higher than the benign group (29% compared to 13%), this difference was not statistically significant. The rate of cancer-related death was 41% in the study by Campbell et al., which was slightly higher than the respective rate in our study. In the study by Perek et al. (14), only 48 patients underwent surgery, 42 of whom survived. Furthermore, in that study, 11 patients received both chemotherapy and surgery. Chemotherapy was exclusively performed for seven patients who had local progression or were affected by retinoblastoma., in our study, three were affected by retinoblastoma, three with hemangioma, three with mature and immature teratomas, and three others with neuroblastoma; one patient with choriocarcinoma died. The worst prognosis rate among malignant tumors was associated with neuroblastoma, in which 3 out of 4 affected infants died. Nonetheless, Campbell et al. (5) revealed that the best prognosis was observed in patients with neuroblastoma tumors. This discrepancy might be due to the difference in disease severity and the applied treatment approach.

Our evaluations indicated that 69.8% of the patients were treated with surgery, five of whom died. From this aspect, those patients who underwent surgery showed the best prognosis for survival. Approximately, 24.5% of the patients underwent pharmaceutical treatment, three of whom died. One patient received chemotherapy and two others underwent both surgery and chemotherapy; two of them died at the end. In the study by Campbell et al. (5), 43 (42%) neonatal cancer patients survived after receiving surgery or radiochemotherapy (or both). Isaacs et al. (18) evaluated clinical and morphological germ cell tumors' differences in fetuses and infants compared to older ones and observed that all the survived cases had undergone surgery for tumor excision. Consequently, according to the current and other similar studies, it seems that the survival rate in the infants undergone surgery is higher compared to other treatment approaches.

The limitations of this study include 1) lack of access to the medical records of the first years of the study despite recording patient's data, 2) having incomplete files that were tried to be completed through the study of clinical procedure and result analysis and confirming them with the Department of Pathology, 3) lack of access to patients' medical history and autopsy results in case the affected child' siblings had died of malignancy before, 4) no access to detailed history taken from parents concerning any exposure to physical and chemical factors during pregnancy, which was resolved through analyzing the files and collecting the necessary information, and 5) unavailibility of the sonographic results and their record's assessment regarding fetal disorders, which was resolved by file analysis.

Conclusion

According to our results, teratoma was the most common tumor among infants admitted to the NICU and the most affected locations were head and neck. Furthermore, neuroblastoma had the highest mortality rate, and survival rate among infants undergoing surgery was higher than those receiving other treatments.

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Conflicts of interests

None declared.

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