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ORIGINAL ARTICLE

Outcome of Pediatric Neuroblastoma at the Children's Hospital and Institute of Child Health, Lahore

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ABSTRACT

Objective: To demonstrate outcome of pediatric neuroblastoma at The Children's Hospital and Institute of Child Health, Lahore.
Study design: Descriptive observational study
Place and duration: The study was conducted in Pediatric Hematology Oncology department, The Children's Hospital and the Institute of Child Health, Lahore in twelve months from March 2020 to February 2021**.**
Methodology: Study was conducted on total of 60 patients of diagnosed neuroblastoma. Main variables of study were age, parent's education, socioeconomic status, traveling distance, LTS, and INSS stage, metastatic sites, tumor size and outcome. SPSS version 23.1 was used for data analysis. Test of significance was applied taking p value ≤0.05 as significant value.
Results: Regarding histopathology, fifty eight 96% patients had neuroblastoma while 4% patients had ganglioneuroblastoma. Life threatening symptoms were present in 85% patients. Most common primary sites were suprarenal 45%, retroperitoneum 25%, pre/paravertebral 11%, posterior mediastinal 11%, others 6%. Metastasis were present in 40% patients at diagnosis and most common metastatic sites were bone marrow 21%, bone 8% and both 10%. Six(10%) patients with stage 2 showed complete remission ,2(3%) partial remission, 2(3%) patients with stage 3 achieved complete remission ,19(34%) partial remission, 4(7%) patients with stage3 expired, 18(30%) patients with stage 4 were put on palliation initially, 2(3%) patients with stage 4S showed complete remission.
Conclusion: The survival outcomes of children with neuroblastoma who were treated at the children hospital lahore between march-2020 and fab-2021are compareable to those in developed and developing countries. A high level of suspicion for neuroblastoma is necessary, especially in children under five years of age with an abdominal mass. This can only be ensured through proper education of health care providers about this aggressive childhood malignancy. Advanced disease presentation is common, high-risk neuroblastoma is considered challenging and has one of the least favourable outcomes among cancers. Late diagnosis due to cultural and socioeconomic barriers and lack of care at primary care level and poor referral to oncology units owing to deficient health care system are still considered the major contributory factors for poor outcome. However, newer treatment strategies are mandated to improve outcomes in pediatric patients who are at high-risk and display relapse. Moreover, multidisciplinary approach with the establishment of infrastructure is the need of time to provide integrated care.
Keywords: Neuroblastoma, Outcome, Management, Children

INTRODUCTION

Neuroblastoma is the most common extracranial tumor among all pediatric solid malignancies (1). The most common site of origin is the adrenal gland but it may arise from any site where sympathetic nervous tissue is present including paraspinal sympathetic ganglia in the chest and abdomen (2, 3). Hereditable gene mutations in the ALK oncogene and a PHOX2B loss-of-function mutation can result in tumors presenting at an early age with severe disease (4-6). Early detection, accuracy in risk stratifications and advanced treatment strategies have improved prognosis.

Neuroblastoma is the most common intra-abdominal tumor in children constituting 8-10% of all pediatric malignancies (7). Treatment depends on risk stratification which in turn is based on age and stage at presentation, histopathological features of the tumor, DNA ploidy, and amplification of the MYCN gene (8, 9). Genetics and biological features of tumors further direct the therapeutic approach, particularly in high-risk cases (7). In developed countries, the outcome varies ranging from over 90% in low-risk cases to as low as less than 50% in high-risk cases (10). In developing countries, neuroblastoma has dismal outcomes as most of the patients present with advanced disease and non-myeloablative therapy can't suffice (11). Delayed presentation, unavailability of diagnostic tools, imprecise risk stratification, inaccessible biological and immunological therapies, lack of autologous stem cell transplant facilities and abandonment lead to poor outcomes (12, 13).

METHODOLOGY

A retrospective observational study was conducted in the department of Pediatric Hematology Oncology, The Children's Hospital and Institute of Child Health, Lahore after obtaining permission from the Institutional Review Board. From March 2020 to February 2021, all newly diagnosed neuroblastoma cases during the study period were included, while all those who had incomplete staging workups, already received treatment, or relapsed cases of neuroblastoma were excluded. Informed consent was obtained from all parents. Initial evaluation included physical examination, CBC, LDH, Sr Ferritin, CT Scan primary site, CT Chest, Mass biopsy and histopathology, B/L BMA, Bone Scan, 24-hour urinary VMA/HVA, and NMYC amplification. Tumors were categorized into low, Intermediate, and high-risk groups based on stage, Age, Nmyc amplification, grade, and life-threatening symptoms. All tumors were further classified based on the International Neuroblastoma staging system (INSS) and International Neuroblastoma Risk Group Staging System (INRGSS) respectively.

In the Pediatric Oncology Unit at The Children's Hospital and Institute of Child Health (CH & ICH), we followed SIOP EUROPE GROUP to treat neuroblastoma. All patients diagnosed with stage L1, L2, and Ms were offered curative treatment, while those with stage M were treated with palliative intent. For stages L1, and L2, treatment modalities included chemotherapy, surgery, and radiotherapy depending on the image-defined risk factor and chemotherapy included carboplatin, Etoposide, Cyclophosphamide, Doxorubicin, and Vincristine. Upfront surgery was offered as a first-line treatment to all patients with stage L1 without the image-defined risk factor.

Data from 60 patients were collected regarding age, gender, education of parents, socioeconomic status, demographic distribution, the lag time for treatment, traveling distance to the children's hospital, tumor site, tumor size, metastatic workup, histopathological finding, 24-hour urinary VMA/HVA, NMYC amplification, and outcome.

In our study , income status was defined as low income (<50000), middle income(>50000), education status as uneducated (never attended school), under matric (education < 10 class), undergraduate (having bachelor study), graduate (having master study), lag times as lag time 1 (time of clinical presentation to time of consultation with GP/consultants, lag time 2 (time of consultation with GP/consultant to time of admission in children

hospital Lahore), lag time 3 (time of hospital presentation to start of treatment), Life-threatening symptoms (intraspinal neuroblastoma , severe pain , vomiting needing IV support, weight loss >10% ,intractable diarrhea with VIP , respiratory distress without infection, respiratory difficulty, increase blood pressure, IVC compression leg oedema, abnormal renal function ,poor urine output, hydronephrosis, deranged liver function , evidence of DIC , thrombocytopenia, bladder/bowel dysfunction secondary to a mass effect, a very large tumour volume with danger of possible tumour rupture)

The data were analyzed using the Statistical Package for Social Studies (SPSS; IBM, version 22 Corporate headquarters 1 New Orchard Road Armonk, New York 10504-1722 United States). The descriptive analysis included mean, standard deviation, median, and range and was computed for age. Frequency and percentage were computed for gender.

RESULTS

Out of 65 patients, 60 newly diagnosed cases of neuroblastoma were included in our study based on inclusion or exclusion criteria. The age of patients ranged from 1 month to 16 years with male predominance and M: F was 1.5:1. Five (8%) out of 60 patients were under 1 year of age while 34 patients(56%) were in the range of 1.5 to 5 years and 15 patients (25%) were more than 5 years of age. Forty-three (71%) patients belong to the rural area and 17 (28%) are from urban areas. In our study population, the Father of 24 (40%) patients and the mother of 38 (63%) patients never attended school. Fifty-six (93%) patients belong to low-income socioeconomic status while 4(6.7%) patients are from middle-income status. Thirty-four (56%) patients had a traveling distance of more than 200KM. Regarding histopathology, fifty-eight (96%) patients had neuroblastoma while 2 (4%) patients had ganglioneuroblastoma. Life-threatening symptoms were present in 51 (85%) patients. Most common primary sites were suprarenal (45%), retroperitoneum (25%), pre/paravertebral (11%), posterior mediastinal (11%), others (6%). Metastasis was present in 24 (40%) patients at diagnosis and the most common metastatic sites were bone marrow (21%), bone (8%), and both (10%). Contributory factors were older age, demographic area, socioeconomic status, father education, LTS, and tumourr size had a significant effect on the INSS stage with a significant ($p<0.050$) p-value.

Table-1: Demographic, socioeconomic and clinical characteristics of patients

Characteristic	Frequency	Percentage
Gender		
Male	36	60.0
Female	24	40.0
Age (years)		
<1	4	8.0
1-1.5	7	11.0
1.5-5	34	56.0
>5	15	25.0
Father education		
Uneducated	24	40.0
Matric	19	31.7
Under Graduation	11	18.3
Graduation	6	10.0
Mother Education		
Uneducated	38	63.3
Matric	12	20.0
Under Graduation	9	15.0
Graduation	1	1.7
Socioeconomic status (thousand)		
<25	51	85.0
25-50	5	8.3
>50	4	6.7
Traveling distance (kilometer)		
<200	26	43.3
>200	34	56.7
Diagnosis		
Neuroblastoma	58	96.7
Ganglioneuroblastoma	2	3.3
LTS		
Yes	51	85.0
No	9	15.0
INSS stages		
2	9	15.0
3	26	43.3
4	23	38.3
4S	2	3.3
Primary site		
Suprarenal	27	45.0
Retroperitoneal	15	25.0
Pre &para vertebral mass	7	11.7
Mediastinal	7	11.7
Others	4	6.7
NYMC amplification		
Amplification	4	6.7
No amplification	29	48.3
Not done	27	45.0
Metastasis		
Yes	24	40.0
No	36	60.0
Metastasis site		
Bone	5	8.3
Bone marrow	13	21.7
Both	6	10.0
No metastasis	36	60.0

Table 2: Association of INSS stages with demographic, socioeconomic and clinical characteristics of the patients

Characteristic	INSS stage				P-value
	2	3	4	4S	
Age (years)					
<1	3	3	1	1	0.038
1-1.5	0	5	0	1	
1.5-5	7	12	15	0	
>5	2	6	7	0	
Gender					
Male	5	16	13	2	0.671
Female	4	10	10	0	
Area of residence					
Rural	7	6	2	2	0.000
Urban	2	20	21	0	
Father education					
Uneducated	1	10	13	0	0.000
Matric	2	10	3	3	
Under Graduation	6	3	2	0	
Graduation	0	3	1	2	
Mother education					
Uneducated	3	17	17	1	0.196
Matric	2	5	5	0	
Under Graduation	4	3	1	1	
Graduation	0	1	0	0	
Socioeconomic status (thousand)					
<25	5	24	21	1	0.016
25-50	3	0	1	1	
>50	1	2	1	0	
Traveling distance (kilometer)					
<200	4	11	10	1	0.997
>200	5	15	13	1	
LTS					
Yes	5	23	22	1	0.016
No	4	3	1	1	
Primary site					
Suprarenal	4	10	12	1	0.854
Retroperitoneal	1	8	5	1	
Pre &para vertebral mass	1	5	1	0	
Mediastinal	2	2	3	0	
Others	1	1	2	0	
Tumor size (cm)					
<5	6	2	0	2	0.000
5-10	2	13	11	0	
>10	1	11	12	0	

Table-3: Association of outcome with demographic, socioeconomic and clinical characteristics of the patients

Characteristic	Outcome					P-value
	Complete remission	Partial remission	Palliation	LAMA	Expired	
Age (years)						
<1	3	0	0	0	2	
1-1.5	1	3	0	0	2	
1.5-5	5	11	14	2	2	0.054
>5	1	7	4	1	2	
Gender						
Male	9	11	11	0	5	0.067
Female	1	10	7	3	3	

Area of residence						
Rural	0	17	17	2	7	0.000
Urban	10	4	1	1	1	
Father education						
Uneducated	0	8	9	2	5	0.130
Matric	3	7	7	0	2	
Under Graduation	4	4	1	1	1	
Graduation	3	2	1	0	0	
Mother education						
Uneducated	2	15	12	2	7	0.107
Matric	3	3	5	0	1	
Under Graduation	4	3	1	1	0	
Graduation	1	0	0	0	0	
Socioeconomic status (thousand)						
<25	5	19	16	3	8	0.133
25-50	3	1	1	0	0	
>50	2	1	1	0	0	
Traveling distance (kilometer)						
<200	6	8	7	1	4	0.777
>200	4	13	11	2	4	
LTS						
Yes	5	19	17	2	8	0.009
No	5	2	1	1	0	
INSS stages						
2	6	2	0	1	0	0.000
3	2	19	0	1	4	
4	0	0	18	1	4	
4S	2	0	0	0	0	
Primary site						
Suprarenal	4	7	8	3	5	0.814
Retroperitoneal	2	6	5	0	2	
Pre &para vertebral mass	2	4	1	0	0	
Mediastinal	2	2	2	0	1	
Others	0	2	2	0	0	
Tumor size (cm)						
<5	9	1	0	0	0	0.000
5-10	1	11	9	1	4	
>10	0	9	9	2	4	
NYMC amplification						
Amplification	0	2	1	0	1	0.650
No amplification	6	10	10	0	3	
Not done	4	9	7	3	4	
Metastatic status						
Metastasis	1	0	18	1	4	0.000
Non metastasis	9	21	0	2	4	
Site of metastasis						
Bone	0	0	4	0	1	0.000
Bone marrow	0	0	11	0	2	
Both	1	0	3	1	1	
No metastasis	9	21	0	2	4	

DISCUSSION

Neuroblastoma is a childhood cancer that manifests a diversity of signs and symptoms. Low-stage tumors are usually well encapsulated and may undergo complete resection with fewer chances of relapse. Contrary to this, high-risk tumors tend to invade local organs, surrounding nerves, and vessels and metastasize to bone marrow, cortical bones, liver, and lungs (1). Despite all advancements and understanding of molecular basis, the prognosis is guarded in cases with advanced presentation as no salvage treatment has been proven to be curative short of bone marrow transplant in developing countries(2). Likewise in our center, NB is challenging with fatal overall survival that emphasizes the need to compute all factors held responsible for advanced presentation thus leading to increased morbidity and mortality.

There is a paucity of data regarding the clinical spectrum and outcome of disease nationwide and no data registry exists. A study by Alia et al conducted in the same center previously, showed male predominance with a median age of 3 years which is precisely comparable with our study and another study by GP Hadley et al (2, 3). In our study population, 56 % of patients presented between 1.5-5years and 25 % above 5 years. Fang X Et al reported that male gender (P=0.04) and advanced age at presentation (P< 0.001) were significant prognostic factors (4).

Our study showed that residing place, education status of the family, and socioeconomic status were significant contributory factors leading to the advanced presentation of the disease. Literature review revealed that Kamahara J et al studied the association between the incidence of NB and socioeconomic status by measuring HDI (human development index) score, a composite measure of life expectancy, anticipated education status, and national standard of living. The correlation was investigated using the Spearman rank correlation coefficient. They concluded their study by narrating a direct relationship between incidence and HDI (5). Another study conducted by Sharma RK et al including 561 patients to investigate the influence of SES and other demographic factors on outcome in Esthisioneuroblastoma (malignant tumor arising from neuroepithelium), reported that race, ethnicity, and SES significantly affected the outcome (6). A Children's Oncology Group study described that high-risk disease was more prevalent in blacks and native Americans (7). While Al-Tonbary Y conducted a study on neuroblastoma patients and observed 76.7% of patients with stage IV disease which is more difficult to treat(7). In our study, localized disease (stage 2) was present in 15% of cases and advanced disease (stage 3,4) in 81% of cases and the most common site was bone marrow about 21.7% of cases. A study in Oman showed that 54.5% were high risk, 35.7% were intermediate risk and 9.8% were low risk. The overall survival rates over five years for the high-risk, intermediate-risk and low-risk groups were 60%, 88%, and 100%, respectively(8) while in our study 6(10%) patients with stage 2 showed complete remission,2(3%) partial remission, 2(3%) patients with stage 3 achieved complete remission,19(34%) partial remission, 4(7%) patients with stage3 expired, 18(30%) patients with stage 4 were put on palliation initially, 2(3%) patients with stage 4S showed complete remission Aforementioned studies prove the effects of biological factors on the outcome of disease thus endorsing the need of population-based data collection.

In our Pediatric Hematology Oncology unit, which is the largest in the country, we receive over 1500 new cases of malignancies every year.

CONCLUSION

The survival outcomes of children with neuroblastoma who were treated at the children's hospital Lahore between march-2020 and February 2021 are comparable to those in developed and developing countries. A high level of suspicion for neuroblastoma is necessary, especially in children under five years of age with an abdominal mass and/or bone pain and irritability or fever with an unknown cause. This can only be ensured through proper education of healthcare providers about this aggressive childhood malignancy. Advanced disease presentation is common, high-risk neuroblastoma is considered challenging and has one of the least favorable outcomes among cancers. Late diagnosis due to cultural and socioeconomic barriers and lack of care at the primary care level and poor referral to oncology units owing to a deficient healthcare system are still considered the major contributory factors for poor outcomes. However, newer treatment strategies are mandated to improve outcomes in pediatric patients who are at high-risk and display relapse. Moreover, a multidisciplinary approach with the establishment of infrastructure is need of time to provide integrated care.

Conflict of interest: Authors declared no conflict of interest.

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