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CLINICAL & BASIC RESEARCH

Neuroblastoma Among Omani Children

Clinical characteristics and survival outcome from a dedicated centre

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abstract: ***Objectives:*** A limited number of publications from the Middle East have focused on neuroblastoma, a common childhood malignancy. This study describes the clinical characteristics and survival outcome of Omani children with neuroblastoma treated at the National Oncology Centre, Oman, between 2010 and 2017. ***Methods:*** From January 2010 to December 2017, data on Omani children aged less than 13 years with neuroblastoma were retrospectively collected. Survival data were statistically correlated with known prognostic factors, including age, stage of disease, MYCN profile and presence of metastasis. ***Results:*** A total of 56 Omani children were included. in this study. The male to female ratio was 1:1. The mean age at presentation was one year and 10 months. The two most common presenting complaints were body masses (48.2%) and constitutional symptoms (33.9%). Approximately, 54.5% were high risk, 35.7% were intermediate risk and 9.8% were low risk. High-risk neuroblastoma was mainly found in children older than one year (76.6%), with low risk mainly observed in children less than one year of age (80%). The overall survival of all groups combined was 74% (P <0.05); the event-free survival (EFS) was 67% (P <0.05). The overall survival rates over five years for the high-risk, intermediate-risk and low risk groups were 60%, 88% and 100%, respectively, and the EFS was 51%, 79% and 100%, respectively. ***Conclusion:*** Omani children with neuroblastoma mainly presented with masses or constitutional symptoms and had an advanced disease at presentation which was associated with inferior survival. The survival outcomes were reasonably similar to published international data.

Keywords: Neuroblastoma; Survival; Event-Free Survival; Oman.

Advances in Knowledge

- *The survival of Omani patients with neuroblastoma is similar to that of other patients in developed countries despite the considerable challenges.*
- *This study highlights the characteristics and management of childhood neuroblastoma in Oman; this information can help to consolidate evidence-based interventions and formulate individualised guidelines for developing countries.*
- *A higher percentage of opsoclonus myoclonus ataxia syndrome as a presentation of neuroblastoma was observed compared to what has been reported in other publications.*
- *Omani patients with neuroblastoma are mainly from the Muscat and Al-Batinah regions which corresponds to the population distribution.*

Application to Patient Care

- *Understanding the clinical presentation of neuroblastoma among Omani children can help in ensuring early detection and improved outcomes.*
- *Elaborating the treatment journey that Omani children with neuroblastoma undertake using current, standard international management guidelines can be useful.*
- *Predicting the outcome based on the stage of the disease upon presentation can be useful.*

Neuroblastoma is an extracranial embryonal tumour that mainly affects children, especially those less than five years of age.[1] It has a challenging treatment protocol and diverse clinical presentations. Neuroblastoma can originate from primitive cells of the sympathetic nervous system in any location in the body.[1] Typically, it occurs in the adrenal medulla or the paraspinal ganglia. Neuroblastoma rarely occurs in adult patients and an increasingly scarce incidence has been noticed in the elderly population.[2]

When neuroblastoma is suspected, an instant biopsy for histopathological and molecular genetic assessment needs to be performed. Other supportive diagnostic tests include urine catecholamines, serum ferritin, lactate dehydrogenase and neuron-specific enolase.[3] Once the tissue diagnosis is established, patients go through staging with bone marrow assessment and nuclear and cross-sectional imaging to identify distant metastases. Neuroblastoma tends to metastasise to different sites, commonly the bone and bone marrow.[3] On rare occasions, it can spread to other sites, including the brain.[4]

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The treatment of neuroblastoma relies on a constellation of specific factors: age, stage, pathology and molecular biology.[5] In accordance with the International Neuroblastoma Staging System (INSS), cases are classified into one of six stages: 1, 2A, 2B, 3, 4 or 4S.[5] In 2009, a newer classification system, the International Neuroblastoma Risk Group (INRG), was established to risk stratify patients into different subgroups based on clinical and prognostic implications.[6] It grouped patients into very low risk (benign histology), low risk, intermediate risk and high-risk categories based on combinations of certain prognostic markers, including the age of the patient (more or less than 18 months), histopathological differentiation and certain biological markers, including MYCN amplification, 11q deletion and the presence of ploidy.[7]

Depending on the risk stratification of the disease, patients undergo either surgery and observation if categorised as low-risk or a lengthy and intense journey of therapy for high-risk individuals. The treatment of high-risk patients includes almost all of the modalities used in the treatment of cancer to date, including conventional chemotherapy, surgery, radiotherapy, autologous bone marrow transplant, immunotherapy and maturation therapy (13-cis retinoic acid).[3]

In the UK, neuroblastoma accounted for 6% of the total new cancer cases in children between 2001 and 2015 with a five-year overall survival rate of 71% from 2011 to 2015.[8] In the USA, the five-year overall survival of the high-risk group was approximately 50% compared to more than 95% for the low- and intermediate-risk groups.[9] Epidemiological records regarding neuroblastoma in the developing world, specifically the Middle East, are scarce. In 2015, a study from Egypt showed that 76.7% of patients had stage 4 disease and the majority were older than one year of age (75.8%).[10] In 2015, a Saudi study of 32 years' worth of data revealed that high-risk children were also the majority (47.6%) and had the worst survival rates.[11] Meanwhile, in a 32-year retrospective study from Iran, most of the children (54%) were in the advanced stage with a 10-year overall survival rate of approximately 58%.[12] Overall, these findings highlighted that the main challenge in neuroblastoma cases in the developing world is the failure of early detection.

Oman is a country on the south-eastern coast of the Arabian Peninsula with a population of approximately 4.5 million.[13] In Oman, children aged less than 13 years with solid tumours receive treatment at the National Oncology Centre, the only oncology centre in the capital of Muscat for the treatment of paediatric solid tumours. Children with different malignancies share the diagnostic and treatment resources with their adult counterparts. This study retrospectively analysed the initial clinical presentation of Omani children with neuroblastoma and the survival outcomes in relation to other prognostic factors which were previously established by recognised international studies.[1,3,5–7] The main challenges faced in the management of neuroblastoma in Oman have also been discussed and some recommendations to improve the outcomes of patients with an aggressive form of the disease have been provided.

Table 1: Characteristics of Omani children with neuroblastoma presenting to and treated at the National Oncology Centre, Oman between 2010 and 2017 (N = 56)

Characteristic	n (%)
Gender	
Male	28 (50.0)
Female	28 (50.0)
Age in weeks	
Mean	174.7
Median	102.1
Range	2–573.6
Histopathology	
Favourable	11 (19.6)
Unfavourable	26 (46.4)
Inconclusive	19 (34.0)
Stage	
1	4 (7.1)
2	2 (3.5)
3	14 (25)
4	31 (55.4)
4S	5 (9.0)
MYCN	
Positive	5 (9.0)
Negative	10 (17.8)
Not done	41 (73.2)
Clinical presentation	
Body masses	27 (48.2)
Constitutional	19 (33.9)
Gastrointestinal	15 (26.8)
Neurological	15 (26.8)
Respiratory	5 (8.9)

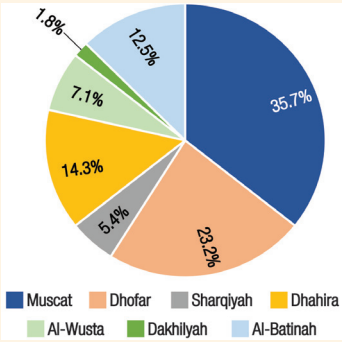

Figure 1: Regional distribution of Omani children less than 13 years of age with neuroblastoma presenting to and treated at the National Oncology Centre, Oman between 2010 and 2017 (N = 56).

Methods

Data were collected from the Royal Hospital Al-Shifa Patient Electronic Record System and inputted into a Microsoft Excel (Microsoft Corp., Redmond, Washington, USA) data collection sheet. Records of all paediatric patients who were diagnosed with neuroblastoma between 2010 and 2017 were obtained from the medical records department. The data were collected exclusively by the study investigators. The diagnosis of neuroblastoma was established with a histological confirmation of the diagnosis following the World Health Organization's (WHO) classification and staging based on the Union for International Cancer Control (UICC). The MYCN amplification was considered positive if neoplastic cells exhibited more than 10 copies using fluorescent *in situ* hybridisation. Staging and risk stratification was done based on the INSS and INRG.[5,6] In the absence of the MYCN testing, risk stratification followed the rest of the parameters in the previously mentioned classification system. All MYCN profiling and autologous bone marrow transplants were done in centres outside the country due to their local unavailability. Patients older than 13 years of age during diagnosis, patients who abandoned treatment, benign histology cases (very low risk) and patients of non-Omani nationality were excluded from the study cohort.

For statistical analysis, the Statistical Package for the Social Sciences (SPSS), Version 22 (IBM Corp., Armonk, New York, USA) was used. Categorised variables were described as percentages and continuous variables were presented as a mean with standard deviation or a median. Proportions were presented as percentages with a 95% confidence interval. The survival rate was illustrated using Kaplan Mayer survival curves. Events for the event-free survival (EFS) were relapses, and those for overall survival (OS) were deaths. This research was granted ethical approval by the Research and Ethical Review and Approval Committee of the Ministry of Health, Oman (SRC#28/2018).

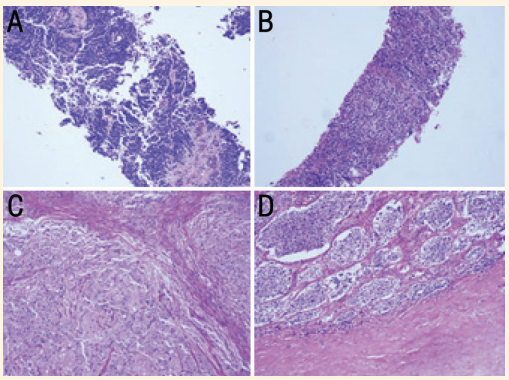

Figure 2: Haematoxylin and eosin stains of the different known histopathological entities of neuroblastoma obtained from Omani patients treated at the National Oncology Centre in Oman. **A:** Undifferentiated neuroblastoma at ×10 magnification showing densely packed small- to medium-sized cells that are indiscernible from a small amount of cytoplasm with vague cytoplasmic borders. **B:** Poorly differentiated neuroblastoma at ×4 magnification showing that ≤ 5% of the tumour cells are differentiating neuroblasts. **C:** Ganglioneuroblastoma or differentiating neuroblastoma at ×20 magnification showing that at least 5% of tumour cells are differentiating neuroblasts. **D:** Residual neuroblastoma at ×20 magnification showing mixed histological combinations.

Results

A total of 56 patients were included in this retrospective analysis. The male to female ratio was 1:1. The regional distribution of the patients within Oman showed that most patients (35.7%) were from Al-Batinah, followed by Muscat (23.2%), while only 1.8% were from Al-Wusta [Figure 1]. This corresponded to the fact that 50% of the population of Oman lives in Muscat and the Al-Batinah coastal plain northwest of the capital.[7] The mean age at presentation was three years and three months, with ages ranging from two weeks to a maximum of 11 years. Children were categorised into three age groups: less than one year of age, as they had shown a better outcome compared to older children in previous studies; one to three years of age; and more than three years old.[14] Patients were also distributed homogenously for significant statistical comparisons. Children were almost equally distributed among the different age groups: 33.9% were less than one year of age, 33.9% were between one and three years of age and the remaining 32.1% were more than three years of age.

Patients were distributed into different INSS groups to determine the appropriate treatment. Overall,

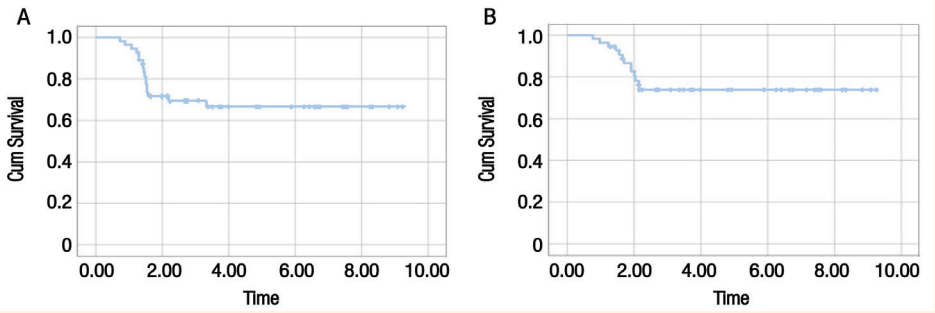

Figure 3: Kaplan-Meier cumulative survival curve showing (**A**) event-free survival and (**B**) overall survival for Omani patients diagnosed with neuroblastoma, presenting to and treated at the National Oncology Centre in Oman between 2010 and 2017.

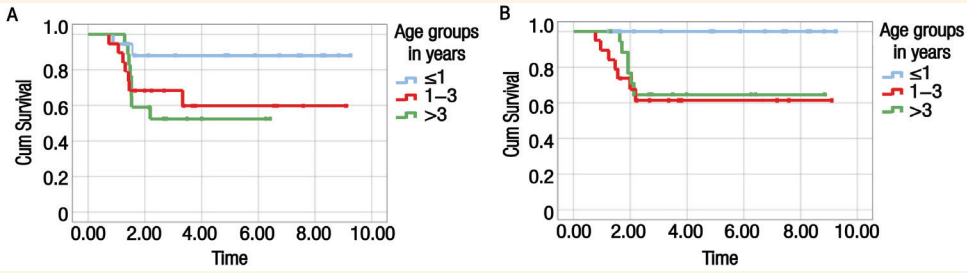

Figure 4: Kaplan-Meier cumulative survival curves showing age-wise distribution of (**A**) event-free survival and (**B**) overall survival for Omani patients diagnosed with neuroblastoma presenting to and treated at the National Oncology Centre in Oman between 2010 and 2017.

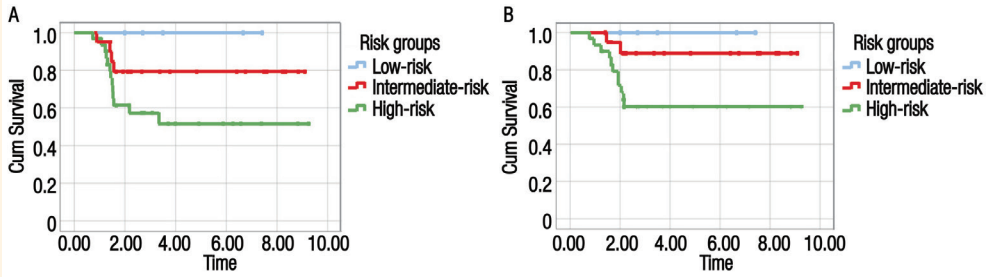

Figure 5: Kaplan-Meier cumulative survival curves according to risk group stratification of (**A**) event-free survival and (**B**) overall survival for Omani patients diagnosed with neuroblastoma presenting to and treated at the National Oncology Centre in Oman between 2010 and 2017.

55.4% were from the stage 4 group, 25.0% were from the stage 3 group, 3.5% were from the stage 2 group and 7.1% were from the stage 1 group, while the 4S group accounted for 9.0% of the total number of patients [Table 1].

Regarding risk, 54.5% were categorised into the high-risk group, 35.7% into the intermediate-risk group and 9.8% into the low-risk group. Among the high-risk group, 23.4% were less than one year of age, 43.3% were between one and three years of age and the remaining 33.3% were more than three years of age at diagnosis. For the intermediate-risk group, 55% were less than one year of age, 40% were between one and three years of age and the remaining 5% were more than three years of age. A total of 80% of the patients in the low risk group were less than one year of age. Most of the patients in the high-risk category were males (63.3%), while most of the patients in the intermediate- and low-risk groups were females (60% and 80%, respectively).

The mean duration of symptoms from the first symptom to the first healthcare visit was approximately 5.25 weeks. Although patients had one major presenting complaint upon their initial clinical encounter, they also had other associated symptoms. The two most common presenting complaints were identification of body masses (48.2%) and constitutional symptoms (33.9%). Masses were specifically described as lumps that were commonly in the abdomen or neck swelling. Constitutional

symptoms included fever, lethargy, excessive crying and poor oral intake which was associated with weight loss. Almost one-third of patients had racoon eye on presentation (28.6%). Additionally, 26.8% had gastrointestinal complaints (e.g. diarrhoea, vomiting and/or constipation) with an equal percentage presenting with central nervous system complaints (e.g. opsoclonus myoclonus, seizures and/or lower limb weakness). The least common symptomatology was respiratory (e.g. shortness of breath) which constituted 8.9% of all presenting complaints.

Subtypes of neuroblastoma included neuroblastoma with opsoclonus myoclonus ataxia syndrome (OMAS; 14.3%) and 4S neuroblastoma (10.7%). Patients with OMAS were predominantly females with a male to female ratio of 1:4. The most common locations were adrenal (55%), followed by paraspinal primaries (22%). Stage 2 and 3 patients constituted 44.4% of the participants each. Approximately, 11.2% of the participants had stage 1 disease and none had stage 4. All of the patients are currently in remission and free of neurological symptoms.

Favourable histology in the form of poorly differentiating or differentiating histological features was seen in 19.6% of the total number of patients [Figures 2A and B]. Unfavourable histology included undifferentiated neuroblastoma [Figure 2C] and constituted 46.4% of the total sample included in this study. Approximately, 34% of the neuroblastoma samples had inconclusive histological characterisation mainly due to a small or inadequate tissue sample size that was insufficient for proper assessment. It was observed that residual tumour pathology could reveal a combination of different histological features [Figure 2D], mainly due to exposure to neoadjuvant therapy.

The most common neuroblastoma site was the suprarenal glands (49%), followed by the paraspinal region (21.4%). Meanwhile, 13.5% of patients had a tumour in the suprarenal gland with paraspinal extension. Other sites included the mediastinum (7.1%), the pelvis and retroperitoneum (3.6%) and the head and neck (5.4%).

In terms of metastasis, the bone was the most common site of involvement, detected in 41% of patients using a meta-iodobenzylguanidine (MIBG) scan, a bone scan or both. The second most common site was the bone marrow (35.7%), followed by the liver (14.3%), lungs (10.7%) and brain (5.4%).

Treatment decisions were based on the constellation of factors making up the risk group of each patient. Patients in the low-risk group were treated with observation after surgical resection. The intermediate-risk group was treated with surgical resection and four to eight cycles of chemotherapy for local control and to prevent spread. The main chemotherapy agents used included carboplatin, etoposide, vincristine, cyclophosphamide and doxorubicin.

The children in the high-risk group underwent an extensive treatment regimen involving six cycles of induction chemotherapy in accordance with the high risk international treatment recommendations.[3] Once the remission status was established through imaging and marrow assessments, local control was resorted to in the form of surgery. Only two patients in the high-risk group did not undergo surgical excision because of the tumour location (one was paraspinal and the other was maxillary). Since 2012, all patients who were eligible for autologous bone marrow transplantation (ABMT) using a busulfan and melphalan conditioning regimen have undergone the procedure. After ABMT, patients were assessed for residual disease after which they received 13-cis retinoic acid (maturation therapy) with the incorporation of radiation therapy for local control at a dose of 21 Gy. Specifically, 63.3% of high-risk patients (a total of 20 patients) underwent a transplant. All patients who went through the transplant received radiotherapy. None of the patients received immunotherapy as it was not available.

The five-year OS and EFS rates for all children during the eight-year study period were 74% and 67%, respectively [Figure 3]. Patients who were 12 months of age and under had excellent OS and EFS rates compared to the rest of the patients (P = 0.029) [Figure 4]. Children between one and three years of age and children older than three years of age had similar OS rates of 61% and 65%, respectively [Figure 4B]. However, the EFS rate of children older than three years of age was 52%, while children between one and three years of age had an EFS rate of 60% [Figure 4A]. The high-risk group had the worst outcome among all groups with a five-year OS rate of 60% and an EFS rate of 51% (P = 0.029) [Figure 5]. The low risk group had an excellent EFS rate and an OS rate of 100% for both, while for the intermediate-risk group, the OS rate was 88% and the EFS rate was 79% [Figure 5].

Discussion

Although neuroblastoma is a massive challenge for paediatric oncologists worldwide, this condition is especially challenging for paediatric oncologists of the developing world for several reasons. First, the affected children typically present late with progressive symptoms and an advanced stage of the disease. In the present study, the average time of presentation was 5.25 weeks which is considered significant for

such a rapidly growing malignancy. Second, ensuring timely pathological diagnosis and staging (specifically, imaging procedures) can be difficult. Third, gathering the proper treatment assets, especially for high-risk patients, can be a huge challenge due to a lack of resources. For example, access to high-dose chemotherapy and immunotherapy might not be possible for some children in the developing world. It has been reported that 73% of patients with neuroblastoma in sub-Saharan African countries had presented with metastatic disease due to a lack of proper medical resources and staging systems.[15] In Oman, access to autologous stem cell transplants was ensured through private or government funds in 2012. However, the delay caused by assigning patients to treatment centres abroad and by having them travel to those centres can impact the outcomes of this already compromised patient population.

The initial symptoms of neuroblastoma, like many other childhood malignancies, can be nonspecific and difficult to detect, especially in younger children and infants. In the present study, almost half of the children presented with body masses (48.2%) and almost one-third also had general constitutional symptoms (33.9%). The combination of these two symptoms is vague and hence can be missed by the primary healthcare system, especially in rural areas lacking resources for measures such as laboratory investigations and imaging. Respiratory compromise due to lung or mediastinal involvement was the least common symptom in the study population (8.9%). This was supported by the fact that the lungs were found to be an uncommon site of metastasis in these patients (10.7%). According to the literature, OMAS is reported in approximately 2–3% of patients with neuroblastoma and is believed to be driven by a paraneoplastic autoimmune process that affects the central nervous system.[16,17] In the present study, 14.3% of the patients presented with OMAS which was higher than the figures presented in other reports in the literature.[16,17] A further study in this subset of patients is recommended to determine why OMAS was more common in the present sample.

In relation to the INRG system, most of the patients in the present study were high-risk (55.4%); this paralleled the results of previous studies where most children presented with high-risk diseases.[18–20] Patients less than one year of age had excellent survival rates which can be explained by the fact that 80% of them were in the low-risk group. The INRG system was used for the patients despite the limitations of tumour genetic analysis.

Staging neuroblastoma requires swift access to cross-sectional and nuclear imaging and tissue examination with a proper histopathological and biological interpretation. With a significant proportion of the people of Oman living in rural areas, proper risk stratification can become compromised. In the present study, 34% of the patients' pathology reports did not classify them into the three known pathological categories: differentiated, poorly differentiated and undifferentiated. Additionally, although MYCN is an established prognostic factor for neuroblastoma outcomes, only 26.8% of the patients were tested. Among the tested samples, 9% were found to be MYCN amplified.[7,21] Since 2018, all Omani patients who are newly diagnosed with neuroblastoma are required to get their tumours molecularly evaluated for MYCN amplification in laboratories abroad. All patients in the present study who had MYCN amplification had a metastatic disease upon presentation. Other important biological markers include deletions of 1p or 11q and an unbalanced gain of 17q which were also not available in the current paediatric oncology treatment centre.[1] The lack of proper molecular genetic assessment in these patients might have led many patients to be undertreated.

This study has several limitations. First, its retrospective nature made it prone to missing information and possible inaccuracies. Another drawback was the small sample size. Despite being the only paediatric oncology treatment centre for solid tumours in the country, the sample might have still not represented all of the Omani paediatric neuroblastoma cases due to a significant number of patients travelling abroad for treatment without seeking any local medical attention

Considering the significant proportion of children who live in remote areas of Oman, access to oncological services can be a significant challenge. In terms of treatment, the local unavailability of autologous stem cell transplant, immunotherapy and local tumour molecular profiling can have detrimental effects on the outcomes of Omani children with neuroblastoma, especially among high-risk patients. Previously, evaluation of the MYCN profile was not done for most patients unless they were diagnosed outside the country in an institution that ran this test. The main reasons were the lack of resources and a probable misunderstanding of the significance of this test. Another major challenge was the lack of adequate diagnostic material for proper pathological classification and the absence of any molecular genetics. This might have subjected the group of high-risk patients to under-treatment and a higher risk for relapse.

Conclusion

The survival outcomes of Omani children with neuroblastoma who were treated at the National Oncology Center between 2010 and 2017 were comparable to those described in the literature in developed and developing countries. Despite the difficulties in diagnosis and management, the results obtained from this study were promising and comparable to published results on international cohorts and they revealed excellent outcomes for intermediate- and high-risk neuroblastoma. However, it was observed that the prognosis for a high-risk disease remains rather poor. Neuroblastoma appeared as non-specific clinical manifestations in the currently studied cohort. 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 health care providers about this aggressive childhood malignancy.

CONFLICT OF INTEREST

The authors declare no conflicts of interest.

FUNDING

No funding was received for this study.

AUTHORS' CONTRIBUTION

AA-B, AmA-R and MM were responsible for data collection. AA-B analysed the data. FAR obtained the pathology data and images. AmA-R and AbA-R performed the statistical analysis. AA-B, AmA-R and FAR drafted the manuscript. AA-B and IA-G reviewed the manuscript before submission. AbA-R and IA-G edited the manuscript. All authors approved the final version of the manuscript.

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