

The Incidence, Clinico-Epidemiological Features, and Prognosis of Neuroblastoma. A Retrospective Study in Al-Imamain Al-Kadhumain Medical City

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ABSTRACT:

BACKGROUND:

The neuroblastoma (NB) burden varies from region to region. Its presentation is variable, and its prognosis is hugely variable.

OBJECTIVE:

The present study aims to evaluate the incidence, clinico-epidemiological characteristics, and prognosis of children with NB receiving treatment and follow-up in Al-Imamain Al-Kadhumain Medical City, a pediatric cancer center.

PATIENTS AND METHODS:

This is a retrospective study involving NB patients managed at Al-Imamain Al-Kadhumain Medical City. The present study was conducted for 14 months between April 2021 and May 2022. The data about age, sex, primary site, metastases, signs and symptoms, staging, and follow-up were extracted from patient files in the hematology and oncology clinic.

RESULTS:

The commonest age was <1 year (55%). The main primary site of the tumor was suprarenal (80%). More than one-third had weight loss, while abdominal mass was reported in 52.5%. The main sites of metastasis were bone marrow and liver (80% and 10%, respectively). The mortality rate was 10%, mainly due to sepsis.

CONCLUSION:

Children under 1 year are the most affected, with a slight female preponderance. The most frequent metastatic sites are bone marrow and liver. The diagnosis depends mainly on bone marrow aspiration.

KEYWORDS: neuroblastoma, oncology, suprarenal, prognosis.

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INTRODUCTION:

Neuroblastoma (NB) is a malignancy growing from neural crest cells^[1]. Genetic defects are probably related to the uncontrolled differentiation and proliferation of neural crest cells^[2].

NB often affects patients in their early years. Children under 5 years old are most likely affected, and male children are slightly more commonly affected than females^[3,4].

NB can arise elsewhere through the sympathetic chain ganglia; however, malignancy often occurs in the medullary region of the adrenal gland^[5].

In general, symptoms and signs of NB vary according to the tumor location and the presence of metastasis. Parents typically observe an abdominal mass in about two-thirds of NS children^[6]. In the advanced stage of illness (stage IVS), weight loss, fever, bone pain, pathological fracture, and periorbital ecchymosis

are common in over half of patients. In rare cases, persistent diarrhea may manifest as a paraneoplastic symptom^[6].

CT scanning is the main method for diagnosing and classifications of neuroblastomas, providing information on tumor origin, extent, presence or absence of lymphadenopathy, presence or absence of metastases, and calcifications^[18].

Urinary catecholamine metabolites, including Vannillyl mandelic acid and Homovanillic acid, are found in 90-95% of neuroblastoma patients, it is useful in diagnosis and treatment response monitoring^[22].

The stages for neuroblastoma are complex and confusing. Staging involve two systems, the international Neuroblastoma Risk Group Staging System (INRGSS) uses results from imaging tests (such as CT or MRI) to decide before the start of treatment decision. The International

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Neuroblastoma Staging System (INSS) is based on the results from the surgery [18]. The International neuroblastoma staging system (INSS) was the most utilized and accepted system over the last thirty years (Table 1).

Table 1: International neuroblastoma staging system (INSS) [7].

Stage	Description
1	Tumor mass with complete resection. No regional lymph node (LN).
2	Tumor mass with incomplete resection or with ipsilateral LN.
3	Tumor mass that crosses midline or with contralateral LN.
4	Distant metastasis.
4s	Patients <1 year, localized tumor mass and metastasis limited to liver, skin, or bone marrow.

Biomarkers are specific alterations at the cellular or molecular level. They are used as a measurable indicator to determine the development of a disease, clinical outcomes, prognosis, and recurrence risk in cancer [19]. MYCN is a proto-oncogene mapped to chromosome 2 (2p24). It is implicated in cell proliferation, differentiation, and apoptosis. The overexpression of MYCN gene resulted in NB development with features similar to that in humans [19]. Tumor cell ploidy is another important prognostic marker in NB, strongly correlated with age, stage, and patient survival, with hyperdiploid or near tridiploid patients showing better outcomes [20]. β -Catenin, a crucial protein for neural crest cell development, is significantly associated with advanced NB stages, metastasis, and poor treatment response [21].

Children with NS have remarkably different outcomes. The most important prognostic factors include age, stage, and biological characteristics of tumor cells [8].

This study aimed to evaluate the incidence, clinico-epidemiological characteristics, and prognosis of children with NB receiving treatment and follow-up in Al-Imamain Al-Kadhumain Medical City, a pediatric cancer center.

PATIENTS AND METHODS:

Study design & settings

A retrospective observational study on patients with neuroblastoma who attended Al-Imamain Al-Kadhumain Medical City, from April 2021 to May 2022.

Participants

This study was done for 14 months. Patients have been diagnosed, treated, and followed up at Al-Imamain Al-Kadhumain Medical City. The records of 40 patients with neuroblastoma who have been managed at pediatric oncology and/or hematology consultation clinics and/or admitted to pediatric hematology or oncology wards between the years 2016 and 2022 (Table 2).

Table 2: Number of neuroblastoma cases diagnosed each year.

Year	Incidence rate of new cases per year
2016	758 cases per 100000 children
2017	?? Missing data
2018	388 cases per 100000 children
2019	371 cases per 100000 children
2020	120 cases per 100000 children
2021	50 cases per 100000 children
2022	25 cases per 100000 children

*No cases were recorded in 2017 due to missing data.

*Case numbers fluctuate significantly across years due to underreporting.

Inclusion criteria

All children with neuroblastoma who were presented to the Hemato/Oncology consultation clinic and \ or admitted to the Pediatric Hemato/Oncology ward in Al-Imamain Al-Kadhumain Medical City.

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Exclusion Criteria

- Refusal of the parents for including their children in the study.
- Those who received treatment outside Iraq and in other centers.

Ethical Consideration

The study is reviewed and approved by local health committee. The parents of every NB child provided written consent before any data collection. The parents were reassured that their data would only be utilized for research purposes. Confidentiality of records was guaranteed.

Clinical examination and data collection

History and clinical examination was done for all the patients and data were collected. The diagnosis of neuroblastoma depends on:

1-Tissue biopsy and histopathological examination of lymph node and abdominal mass.
2-Bone marrow aspirate and the presence of suprarenal mass plus positive urinary catecholamines (Vanillyl mandelic acid and Homovanillic acid).

3-Mass resection and histopathological examination of resected mass.

4 -Imaging studies: CT scan, MRI, abdominal ultrasound, standard skeletal survey.

5-Fine needle aspiration (FNA) and pathological exam of the mass.

All patient data were subjected to the refinement of age, sex, residence, site of primary disease, metastases, signs, and symptoms. Staging according to the international neuroblastoma study group (INSS), risk group (depending on age and staging at diagnosis), response to treatment (chemotherapy), outcome, and follow-up were taken from the recording files in the Hemato-Oncology Clinic.

Data analysis

Data collection, revision, and coding were all done. The Statistical Package for Social Science (IBM SPSS) version 25 (SPSS Inc., Chicago, Illinois, USA) was used for statistical analysis. The quantitative data were represented as mean and standard deviations (SD). Additionally, qualitative data were also represented as numbers and percentages. The chi-square test was used to compare the qualitative data between the groups. A student's t-test was used to compare groups based on quantitative data with a parametric distribution.

RESULTS:

Demography of patients

370 patients were diagnosed with a malignancy between the years 2016 and 2022, 40 of whom were diagnosed with neuroblastoma(Figure 1).

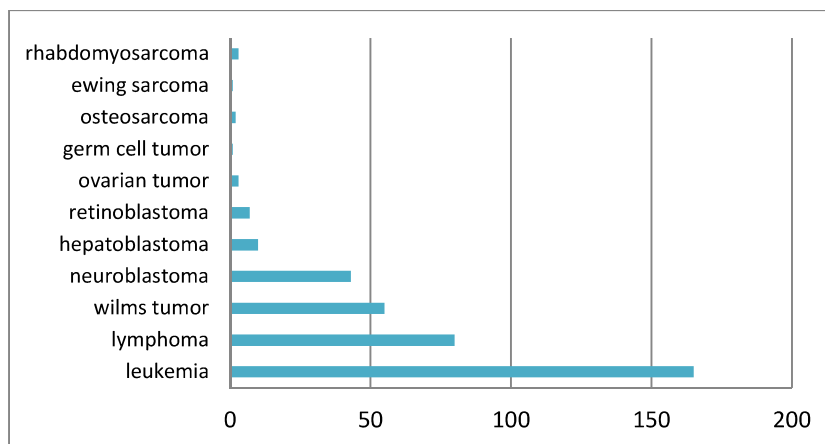


Figure 1: Patient diagnosed with different types of malignancies.

The most common age was <1 year (55%), followed by the age group 1-5 years (42.5%). Finally, one patient was >5 years old (2.5%).

Females were more common than males (57.5% versus 42.5%). The female-to-male ratio was 1.35:1(Table 3).

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Table 3: Demographic characteristics of children with neuroblastoma(NS).

Variables		Number	Percentage
Age, years	<1	22	55%
	1-5	17	42.5%
	>5-14	1	2.5%
Sex	Male	17	42.5%
	Female	23	57.5%
Total		40	100%

Clinical symptoms and signs

More than one-third (35%) had weight loss, while abdominal distension was reported in 30%. Less common symptoms were fever (10%). Bone pain, walking difficulties, and diarrhea were reported in 2 patients (5%). Abdominal mass was the most common sign reported (52.5%),

followed by failure to thrive, abdominal mass (20%), and pallor (12.5%) (Table 4).

The most common primary site of tumor was suprarenal encountered in 32 patients (80%), followed by retroperitoneal (5 patients, 12.5%), paraspinal (2 patients, 5%), and cervical (1 patient, 2.5%).

Table 4: Clinical symptoms and signs of neuroblastoma at presentation.

Variables		Number	Percentage
Symptoms	Weight loss	14	35%
	Abdominal distension	12	30%
	Fever	4	10%
	Bone pain	2	5%
	Walking difficulties	2	5%
	Diarrhea	2	5%
	Chest symptoms	1	2.5%
	Scalp swelling	1	2.5%
	Urine retention	1	2.5%
	Pathological fracture	1	2.5%
Signs	Abdominal mass	21	52.5%
	Failure to thrive	8	20%
	Pallor	5	12.5%
	Ecchymosis and petechial rash	3	7.5%
	Proptosis and raccoon eyes	2	5%

*Some patients had more than one symptom or sign.

Diagnostic procedures

Bone marrow aspiration was positive in 32 patients (80%). Mass resection was performed

for 6 patients. Alternatively, one patient had fine needle aspiration, and another patient had an excisional lymph node biopsy (Table 5).

Table 5: Diagnostic procedures for neuroblastoma.

Procedure	Number of patients	Percentage
Bone marrow aspiration	40(32 were positive)	80%
Mass resection (excisional)	6	15%
Fine needle aspiration	1	2.5%
Lymph node biopsy(excisional)	1	2.5%

Histopathological types

In the majority of patients (85%) histopathology was not available. However, the tumor was well

differentiated (66.6%), and undifferentiated (33.3%) (Figure 2).

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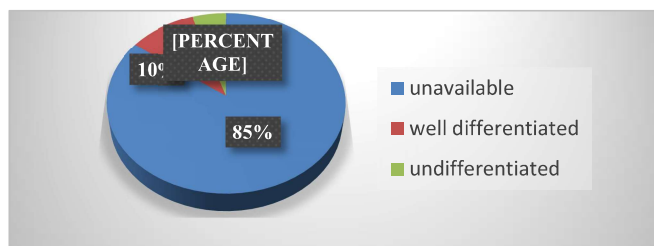


Figure 2: Histopathological types of neuroblastoma

Tumor staging

The tumor was in stage IVS (55%), and stage IV III were found in 8 patients (20%) (Figure 3). (25%) while tumors in Stage

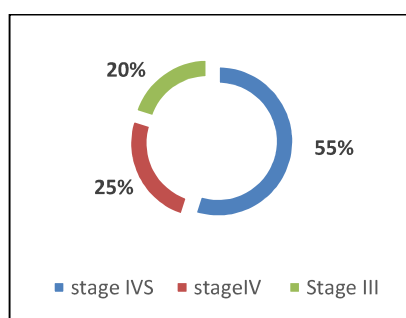


Figure 3: Tumor staging of neuroblastoma.

Site of metastasis

The Bone marrow and liver are the major site of metastasis (80% and 10%, respectively) (Table 6).

Table 6: Sites of metastases.

Site of metastasis	Number	Percentage
Bone marrow(only)	32	80%
Liver	4	10%
Bone	2	5%
Skull	1	2.5%
Skin	1	2.5%

*Some patients have more than one site for metastasis.

Outcome

Seventeen patients (42.5%) have survived and finishing chemotherapy. Eight patients have lost are off treatment, followed up for 5 years. followers (20%), while 4 patients (10%) However, 11 patients (27.5%) relapse after unfortunately died (Table 7).

Table 7: The outcome of children with neuroblastoma.

Outcome	Number	Percentage
Survived and off treatment(Observed in 5 years duration)	17	42.5%
Relapse after finishing chemotherapy and still on treatment	11	27.5%
Lost	8	20%
Died	4	10%
Total	40	100

The main cause of death was sepsis (50%).

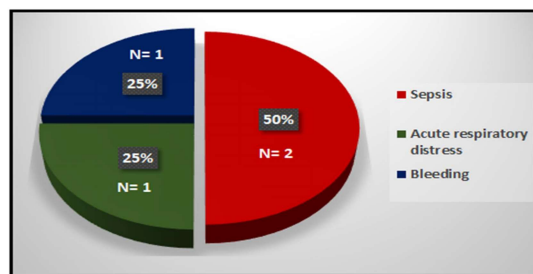


Figure 4: Causes of death in children with neuroblastoma.

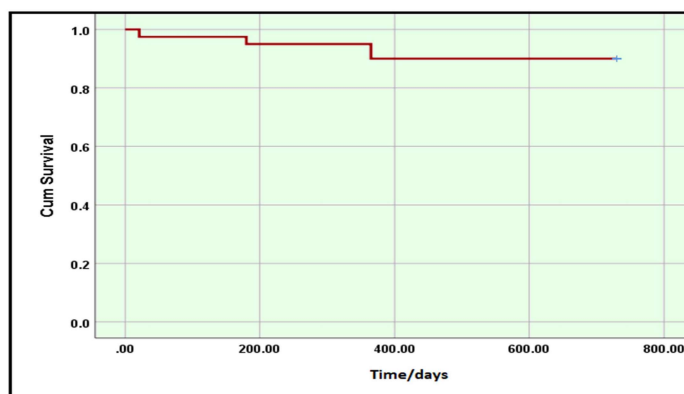


Figure 5: Kaplan-Meier curve showing overall survival.

Overall survival(OS) was considered to be The length of time that passed between the diagnosis and death.

DISCUSSION:

It can be challenging to identify the symptoms and signs of NS because it is a rare cancer and because its clinical picture is quite similar to that of other common pediatric diseases [9]. The goal of the present study is to assess the incidence, clinico-epidemiological features, and prognosis of patients with NS.

The present study found that the age group <1 year was the most commonly affected (55%). The incidence falls among the age group of 1–5 years (42.5%). The female-to-male ratio was 1.3:1.

Different studies worldwide presented different epidemiological characteristics. Sutaryo et al. [10] evaluated the clinical profiles of Indonesian children (40 patients) with NS. The age group (1–5 years) was commonly affected (65% of the cases), while the age group < 1 year represented 15% of the patients. The male-to-female ratio was 1.5:1. The median age of NS, as reported by Al-Tonbary et al. [11], was 30 months, with 24.2% of patients being <1 year and 75.8% being ≥1 year at the time of diagnosis. The male-to-female ratio was 1.06. Furthermore, previous findings show that 40% of neuroblastoma cases

occur in the first year of life [12]. This can be explained as the neuroblastoma being driven by the fetal neuroblast cells.

In the present study, suprarenal was the primary site in 80% of cases followed by retroperitoneal (12.5%). Al-Tonbary et al. [11] reported that the most common site of the primary tumor was the suprarenal glands (72.7%), followed by retroperitoneal (15.1%). According to the SEER monograph study, the adrenal gland was the most common site for primary tumors [13]. In Saudi Arabia, a study of NS patients for 10 years revealed that the main site for the primary tumor was the adrenal and retroperitoneum [14].

In the present study, the most common symptoms in patients with NS were weight loss and abdominal distension (35%, and 30%, respectively). The most common sign was abdominal mass (52.5%). In a Brazilian study involving 258 patients, Lucena et al. [15] reported that the most common symptoms and signs were fever (25%), abdominal pain (22%), and abdominal mass (19%). The discrepancies throughout the different studies could be explained by variations in demographic characteristics and the presence of comorbidities. In the present study, 80% of the cases were diagnosed by bone marrow aspiration, while mass resection was used in 15% of cases.

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Worldwide; most previous studies used only one or two diagnostic techniques. Sutaryo et al. [60] used biopsy for 23 cases; the rest were diagnosed based on examination of bone marrow aspiration. In an Iranian study, all cases were diagnosed with immunohistochemistry [16].

In the present study, the vast majority of cases were either stage IVS (55%) or stage IV (25%). The findings are in line with the findings of Mora et al. [17], who reported that the majority of NS cases presented with late-stage disease. The high rate of late-stage diagnosis could be explained by the delayed diagnosis of this rare cancer.

In the present study, the most frequent sites for metastasis were bone marrow (80%) and liver (10%). Al-Tonbary et al. [11] reported that 85.7% of cases developed metastasis. Similarly, in the Iranian study, bone and bone marrow were the most common sites of metastasis (55.9% and 48.6%, respectively) [16].

In the present study, 42.5% of patients survived, 27.5% relapsed after chemotherapy, and 10% unfortunately lost. The major cause of mortality was sepsis. When compared to other studies, the survival rate is high. The survival time in the Egyptian study was 19.4–29.4 months [11]. In the Indonesian study, 20% of patients survived, 37.5% died, and 42.5% were lost to follow-up [10]. The variation in the survival rate between different studies is logical because there are different follow-up periods and different patient characteristics.

In an Egyptian study, the study included 136 patients, 67 males and 69 females. The three-year overall survival (OS) was 94% ± 2%. Overall survival varies according to gender, age, and pathology. Elzomor et al. concluded that there is high rate of survival is currently achievable in patients with intermediate-risk neuroblastoma by chemotherapy or chemotherapy and surgery [23].

Few studies in Saudi Arabia have been performed to determine the survival rate of neuroblastoma in children. Naqib et al. (2015) observed 42 patients for 8 years. The overall survival rate was 71.5%. Among those who were <1 year of age at presentation was 82%, whereas the ≥1 yr age group had 62% survival rates. Patients with tumors in the adrenal had considerably low OS (63%) when compared to patients with tumor sites other than the adrenal (OS of 89%) ($p < 0.05$). Naqib et al. concluded that there are excellent outcomes for stages 1, 2, and 3 and poor prognosis for stage 4 [24].

Regarding the cost-effectiveness of treatments such as chemotherapy, surgery, or supportive

care, all investigations and treatments are provided free of charge at our center, with no financial burden on families or barriers to accessing advanced treatments.

This study is a single-center, small-scale, cost-effective, and easier-to-conduct. Still, it may recruit too few patients, posing a risk of insufficient participants for generalization, necessitating more extensive multicenter studies.

CONCLUSION:

Children under 1 year are the most affected by NS, with a slight female preponderance. The primary tumor was frequently found suprarenal. The most frequent metastatic sites are bone marrow and liver. The diagnosis of NS depends mainly on bone marrow aspiration.

Recommendations

A large multicenter study is required to allow diverse population and generalization of the results.

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