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Original Article

A five-year review of children with neuroblastoma at Dr. Sardjito General Hospital, Yogyakarta, Indonesia

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Abstract

Background Neuroblastoma is the third most common tumor in children, after leukemia and retinoblastoma. The disease presents with a wide range of symptoms.

Objective To assess the clinical profiles of children with neuroblastoma at Dr. Sardjito General Hospital from 2012-2016.

Methods A retrospective review of all children with neuroblastoma under 18 years of age in the Children's Ward of Dr. Sardjito General Hospital, Yogyakarta from 2012-2016. Patients diagnosed and treated in other hospitals were excluded. Data were taken from the *Yogyakarta Pediatric Cancer Registry* (YPCR) and medical records. Outcomes were assessed by patient status: alive, died, or lost to follow-up.

Results A total of 40 subjects were included in this study. Six (15.0%) patients were diagnosed at <1 year of age, 26 (65.0%) patients at 1 to <5 years of age, 6 (15.0%) patients at 5 to <10 years of age, and 2 (5.0%) patients at ≥10 years of age. The male to female ratio was 1.5:1. Four (10.0%) patients had stage IV-S, 34 (85.0 %) patients had stage IV, and 2 (5.0 %) patients had stage II/III of the disease. Proptosis (40.0%) and abdominal mass (35.0%) were the most common chief complaints. Eight (20.0%) patients were alive at the end of observation, 15 (37.5%) died, and 17 (42.5%) were lost to follow-up. The deaths were mostly caused by sepsis.

Conclusion Most patients are diagnosed at the age of 1 to <5 years, with a median age of 3 years. Proptosis is the most common chief complaint. Most patients present in stage IV. Overall survival rate is very low. The high numbers of lost to follow-up should be noted. **[Paediatr Indones. 2019;59:157-63; doi: http://dx.doi.org/10.14238/pi59.3.2019.157-63]**.

Keywords: *neuroblastoma; pediatric; overall survival*

Neuroblastoma, an embryonic malignant tumor originating from the neural crest, is the third most common tumor in children after leukemia and retinoblastoma.[1] Each year, approximately 1,500 cases occur in Europe and 700 in the United States and Canada, accounting for about 28% of all cancers diagnosed in European and United States infants.[2,3] Its incidence peaks in infancy and then drops by half in the second year of life.[2] Cancer registries in developing countries are few and often insufficient for a number of reasons, not the least being lack of sustained funding and infrastructure, as well as absence of the recognition of cancer as a national health care priority.[3] A hospital-based registry, *Yogyakarta Pediatric Cancer Registry* (YPCR), has been ongoing in the Department of Child Health, Dr. Sardjito Hospital, Yogyakarta, Indonesia since 2000.1 There is a severe lack of information on pediatric cancer epidemiology in developing countries, which face such challenges as unreliable census data, under-reporting of cases, inaccurate diagnoses, and no

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certified documentation of deaths.[2] This study aimed to determine the clinical profiles of children diagnosed with neuroblastoma in Dr. Sardjito General Hospital from 2012-2016.

Methods

A retrospective review was conducted of children with neuroblastoma under 18 years of age in the Children's Ward of Dr. Sardjito General Hospital, Yogyakarta from 2012-2016. Patients diagnosed and treated in other hospitals and those with incomplete medical records were excluded. Data taken from the YPCR and medical records included age, sex, stage of disease, address, paternal education level, and clinical presentation. Diagnoses were based on diagnostic radiology test, biopsy, bone marrow aspiration, and laboratory tests, including vanillylmandelic acid (VMA), lactic dehydrogenase (LDH), and ferritin measurements. Risk stratification was assessed based on *International Society of Paediatric Oncology - Pediatric Oncology in Developing Countries* (SIOP-PODC) adapted risk stratification for low- and middle-income settings. Outcomes were assessed by patient status: alive, died, or lost to follow-up.

Descriptive data are presented in the text and tables. Patients were contacted by phone if they had not returned by June 30th 2017. Patients who could not be reached by phone were considered lost to follow up. Lost to follow-up patients were excluded from assessment of overall survival. Survival was measured from the date of diagnosis to the date of death or of the last follow-up appointment. Overall survival (OS) was estimated using Kaplan-Meier curves. Analyses were done using *SPSS version 25 for Windows* software.

Results

In total, 41 cases of neuroblastoma were identified from the hospital records between 2012 and 2016. One case was subsequently excluded due to the patient's diagnosis and treatment in another hospital. The disease incidence peaked in the 1-<5 years age group (**Table 1**), with a median age of 3 years at the time of diagnosis. Proptosis (40%) and abdominal enlargement (35%) were the most common chief complaints (**Table 2**). Most patients presented in stage IV (85%). All clinical presentations are shown in **Table 2**. Nine (22.5%) patients presented with bone metastases only, 8 (20.0%) patients with bone marrow metastases only, and 4 (10.0%) patients with bone, bone marrow, and intracranial metastases (**Table 3**). Thirty-four (85.0%) patients had primary tumors in the abdominal region, 26 of which arose from the adrenal medulla. Two primary tumors were found in the thorax and one in the pelvic region. There were three cases with unknown primary tumor region.

Table 1. Characteristics of subjects

Characteristics	(n=40)
Age at diagnosis, n (%)	
<1 year	6 (15.0)
1 to <5 years	26 (65.0)
5 to <10 years	6 (15.0)
≥10 years	2 (5.0)
Sex, n (%)	
Male	24 (60.0)
Female	16 (40.0)
Stage, n (%)	
I	0 (0)
II and III	2 (5.0)
IV	34 (85.0)
IV-S	4 (10.0)

Table 2. Clinical features

Clinical features	Number of patients
Chief complaints	
Protruding eye	16
Abdominal enlargement	14
Walking difficulties/ bone pain	7
Lump in waist	1
Pale	1
Testicular enlargement	1
Clinical presentation	
Pallor	38
Weakness	37
Loss of appetite	34
Abdominal mass	27
Hepatomegaly	25
Lymphadenopathy	26
Raccoon eye	23
Fever	23
Splenomegaly	16
Head lump	15
Walking difficulties	15
Bleeding	10
Pleural effusion	9
Others	3

Twenty-three (57.5%) patients underwent biopsy, and only 12.5% underwent immunohistochemistry (IHC) examination. The VMA, LDH, and ferritin examinations were done in less than 50% of patients (**Table 4**).

Chemotherapy regimens consisted of vincristine 1.5 mg/m^2 and cyclophosphamide 600 mg/m^2 on first day, cisplatin 80 mg/m^2 on the second day, and etoposide 200 mg/m^2 on the third day. Chemotherapy was given for 8 cycles, with a 3-week interval between each cycle. Fifteen (37.5%) patients were died at the end of the observation and 17 (42.5%) were lost to follow-up. The deaths were mostly caused by sepsis (6 cases) (**Table 5**). Most of the lost to follow-up patients did not return to continue treatment. Most of patients came from other provinces (60.0%) (Table 1) and lacked communication access, so it was difficult to trace them.

Table 3. Metastases sites

Site	(N=40)
Bone	9 (22.5)
Bone marrow	8 (20.0)
Bone and bone marrow	5 (12.5)
Bone marrow, intracranial, and bone	4 (10.0)
Bone and intracranial	2 (5.0)
Bone marrow and intracranial	1 (2.5)

Table 4. Diagnostic procedures

Type of diagnostic procedure	(N=40)
Biopsy	
Yes	23 (57.5)
No	17 (42.5)
IHC	
Yes	5 (12.5)
No	35 (87.5)
Bone marrow aspiration	
Positive	18 (45.0)
Negative	17 (42.5)
No	5 (12.5)
VMA level	
≤8 mg/24 h	15 (37.5)
>8 mg/24 h	1 (2.5)
No	24 (60.0)
Ferritin level	0 (0)
<120 ng/mL	5 (12.5)
≥120 ng/mL	35 (87.5)
No	
LDH level	
<750 IU/mL	2 (5.0)
≥750 IU/mL	7 (17.5)
No	31 (77.5)

Table 5. Cause of death

Cause of death	Number of patients
Sepsis	6
Intracranial metastases	2
Pulmonary metastases	2
Pulmonary edema	2
Abdominal compartment syndrome	1
Acute respiratory distress	2

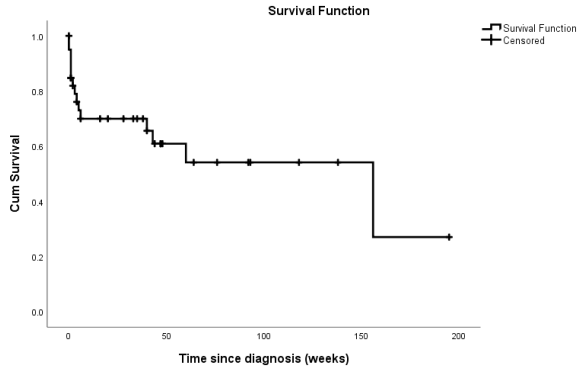

Figure 1. Overall survival

Survival analysis was carried out on 40 patients. Our overall survival was 27.1% (**Figure 1**). It demonstrated that the survival rate was low, especially in our hospital from 2011-2016.

Discussion

Neuroblastoma represents 5.5% of all malignant diseases in children in the Department of Child Health, Faculty of Medicine Universitas Gadjah Mada/Dr. Sardjito General Hospital, Yogyakarta.[1] Neuroblastoma is the third most common type of cancer in children, after leukemia and retinoblastoma.[1,4,5]

Previous reports indicate that 40% of neuroblastoma cases occur in the first year of life, 35% between the ages of 1 to 2 years, and 25% after the age of 2 years.[6,7] In our study, 15.0% of cases occurred at <1 year of age. The percentage of patients with neuroblastoma in the 1 to <5 year age group was most prevalent (65%), compared to other age groups. In a previous study, the median age at diagnosis was 2 years and 90% of cases were diagnosed before the age

of 5 years.[8] The median age diagnosed in our study was 3 years. Neuroblastoma is more common in boys than girls with a ratio of 1.1: 1 to 1.5: 1.9.9,10 Our study had a male: female ratio of 1.5:1.

Protruding eye and abdominal distension were common chief complaints, involving 16 (40.0%) and 14 (35.0%) cases, respectively. Walking difficulties or bone pain were observed in 7 (17.5%) cases, indicating the presence of bone metastases or spinal compression.[11,12] Pallor and weakness were also common accompanying symptoms, with 38 (95.0%) and 37 (92.5%) cases, respectively, followed by decreasing appetite in 34 (85.0%) and abdominal mass in 27 (67.5%) cases. Bansal *et al.* reported 103 cases with neuroblastoma in India and found fever in 67 (65%) cases, abdominal distension or abdominal pain in 56 (54.4%) cases, bone pain in 32 (31%) cases, proptosis in 28 (27.2%) cases, paresis of lower extremity and urinary incontinence in 2 cases each, jaundice in 3 cases, and chronic diarrhea, hematuria, abnormal gait, and abnormal eye movement in one case each. On physical examination, they found hepatomegaly in 31 cases (30%), bone lesion in 26 (25.5%), splenomegaly in 15 (14.6%), lymphadenopathy in 14 (13.6%), central nervous system metastases in 7 (6.8 %), bilateral pleural effusions in 4 (3.9%), and superior vena cava syndrome with opsomyoclonus and ataxia in one case.[13] In our study, there were no cases of opsomyoclonus, ataxia, or superior vena cava syndrome. Opsomyoclonus and ataxia are often associated with good prognoses.[14,15]

Instead of history-taking and physical examination, the diagnosis of neuroblastoma is based on either small round blue cells in the tumor biopsy or by identification of rosette cells in the bone marrow.[16,17] Urine catecholamine test is recommended.[18] Biopsy can be done in the primary tumor or sites of metastases.[19] In our study, biopsy was done in 23 (57.5%) cases; the rest were determined based on examination of bone marrow aspiration and/or CT scan. Immunohistochemistry staining that may be used includes neuron-specific enolase, tyrosine hydroxylase, CD-56, and synaptophysin.[20,21] In our study, only 5 patients had immunohistochemistry staining and 16 (40.0%) had VMA examinations. Of these 16 patients, only 1 patient had an abnormally high level. The sensitivity of VMA was reported to be 80.7%, but increased to 91.2% when combined with HVA.[22] The levels of VMA and HVA are considered to be high if above 2.5 SD based on levels in healthy children of an age-matched.[23]

Most primary tumor sites were found in the adrenal medulla (61.5%). The rest were unknown. Metaiodobenzylguanidine (MIBG) scintigraphy has high sensitivity and specificity (88% and 99%, respectively) in defining tumor sites, both primary and recurrent.[19,24] The MIBG scintigraphy is also recommended for metastases of disease.15 However, this modality is currently unavailable in our hospital.

In our study, 85.0% patients presented with stage IV, a late stage of disease. Unspecific signs and symptoms are some of the causes for late presentation.[11] Bone metastases were found in 45.0% of our patients. Metastases are mostly found in long bones and skull, bone marrow, liver, lymph nodes, and skin.[11,25] Pulmonary and intracranial metastases are rarely seen, although there is often hematogenous spreading.[8] We found pulmonary metastases in 2 (5%) cases and both of them died. Of 7 patients with intracranial metastases, 4 died and the others were lost to follow-up.

Risk stratification is defined by Shimada histology, MYCN, *International Neuroblastoma Pathologic Classification* (INPC) classification, and 11q aberration.[26] Most developing countries do not have these standard examinations. As a result, in 2015, *International Society of Paediatric Oncology - Pediatric Oncology in Developing Countries* (SIOP-PODC) created risk stratification guidelines for low-middle income countries with limited resources. That classification uses *International Neuroblastoma Staging System* (INSS), initial status, age, LDH level, ferritin level, and MYCN status (if known).[16] In our study, 33 cases were high risk.

Increasing LDH is a strong prognostic indicator of poor outcome and correlates with unfavorable histology.[26,27] Patients with LDH >1,300 IU/mL have 12.9 times greater risk for relapse.[28] *International Neuroblastoma Risk Group* (INRG) found that LDH level more than 587 IU/mL has poor prognostic. High level of ferritin correlates with low event-free survival (EFS), but positively associated with stage.[20] The LDH and ferritin levels are not included in the INRG stratification because of lack of specificity. The SIOP-PODC risk stratification using LDH and ferritin

levels with thresholds of 750 IU/mL and 120 ng/mL, respectively.[16]

The patients with the worst prognoses are children aged >15 months, those at an advanced stage, and those testing positive for several molecular biology markers such as MYCN. The V-myc avian myelocytomatosis viral oncogene neuroblastoma derived homolog (MYCN) is an oncogene for regulating cell proliferation and apoptosis.[29,30] The MYCN is positive in 5-10% cases in children under 12 months and 20-30% cases in later ages.[2] Overall survival in developed countries has increased, along with the use of intensive therapy.[31,32] Five-year overall survival in the United States and Europe is 58%, but only 10% in developing countries.[33,34] In our hospital from 2000 to 2004, the OS was 20%.[35] Our study revealed overall survival rate was 27.1%. Fifteen (37.5%) patients were died at the end of the study and 17 (42.5%) were lost to follow up. The deaths were mostly caused by sepsis (6 cases).

Of the 15 patients who died, four did not receive therapy. They presented with abdominal distention, bone metastases, intracranial metastases, and pulmonary metastases. Seven patients died in the first cycle of chemotherapy. They also presented with multiple site metastases. Patients with poor clinical condition could not tolerate the side effects of chemotherapy agents. Palliative chemotherapy should be used in these cases.[15] Four patients died after receiving complete chemotherapy. Three patients had progressive disease and intracranial metastases. One patient had no response to treatment and died because of sepsis.

The cause of loss to follow up was patients not returning to continue therapy. It was difficult to trace these patients' latest conditions because of lack of communication access and distant home addresses. Twenty-four (60.0%) patients lived in the outer areas of Yogyakarta Province, as Dr. Sardjito General Hospital is a referral hospital from all parts of the province. Communication access was difficult because the phone numbers provided were not active and some were phone numbers of village officials who had accompanied the patients.

In conclusion, neuroblastoma is one of the most common tumors in children. Most patients are diagnosed at 1-<5 years, with a median of 3 years. Proptosis is the most common chief complaint. Most patients (85.0%) present in stage IV. Overall survival is very low. The high number of patients lost to follow up should be noted.

Conflict of Interest

None declared.

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