Profile of Neuron-Specific Enolase, Lactate Dehydrogenase, Fine Needle Aspiration Biopsy, and Bone Marrow Aspiration Examination to Diagnose Neuroblastoma Patients in Hematology Oncology Division of Pediatric Department at Dr. Soetomo General Hospital

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ABSTRACT

Background: Neuroblastoma is a malignant solid tumour in children which attacks sympathetic nervous system. Despite of increment in its number of incidence, it is still rarely investigated. This research aims to improve the understanding of neuroblastoma based on the profile of patients, and further, to improve services for patients.

Methods: This was a retrospective study conducted by assessing and descriptively analyzed patients medical record.

Results: From 52 patients, 56% were male and 71% were between age of 1-5 years. Neuron Specific Enolase (NSE) examination showed that most patients had high levels in 29 patients (56%) while Lactate Dehydrogenase (LDH) examination showed that 23 patients (44%) had low levels. Based on Fine Needle Aspiration Biopsy (FNAB) examination, 22 patients (42%) showed formation of malignant round cell tumor. Meanwhile, through Bone Marrow Aspiration (BMA) examination, it was found that the tumors had already spread to bone marrow in 17 patients (33%).

Conclusions: Based on tumor markers and pathological finding, this study revealed that the majority of neuroblastoma patients had poor prognosis.

INTRODUCTION

Neuroblastoma is an embryonal tumor on the sympathetic nervous system that emerged in the early fetal and post-natal fetus from sympathetic cells derived from the neural crest (1,2). Neuroblastoma is the most common extracranial solid tumor in childhood that is often diagnosed during the first 10 years of life, and is responsible for 11% of pediatric cancer deaths in patients younger than 15 years of age (3).

Since 1984, Japan is the only country which held mass screening as a national policy for neuroblastoma. But after studies from Germany and Canada in 2002, a mass screening for neuroblastoma showed no mortality reduction and then it was being halted (4). So, universal screening has not detected poor prognosis disease in general (5).

There are around 11000 childhood cancer cases each year in Indonesia. Based on the Early Detection Installation and Health Promotion of Dharmais Cancer Hospital, there were 15 new cases and 7 deaths with neuroblastoma from 2010-2013. In developing countries like Indonesia, the prognosis in children diagnosed with cancer is much slower. Inadequate equipment and drugs in hospitals, the occurrence of complications of the disease, and the lack of knowledge related to cancer in primary health care providers can affect the effectiveness of cancer treatment (6).

Neuroblastoma is a solid tumor characterized with spectrum of histopathologic features and heterogeneous clinical phenotypes. Accurate clinical staging and risk assessment based on clinical, surgical, biological and pathological criteria are of pivotal importance in assigning prognosis and planning effective treatments. To specify patient’s prognosis and
outcome, plenty of studies have analyzed the presence of several clinicopathological and biological factors related to neuroblastoma (7).

Data on tumor markers and pathological findings from neuroblastoma patients in developing countries are rarely reported, even though the number of patients is quite large. This study was conducted to provide observation of the characteristics of tumor markers and pathological findings in neuroblastoma patients to determine patient’s prognosis and outcome.

METHODS

This research is a retrospective descriptive study. It focuses on prevalence of neuroblastoma case distribution by observation of the medical records. The study was approved by the ethics of Dr. Soetomo General Hospital Surabaya with number of ethics letter 599/Panke.KKE/XI/2015 on December 3rd 2015. There was no conflict of interest between researchers.

Instruments used in this research were medical records of neuroblastoma patients in Hematology Oncology Division of Pediatric Department in Dr Soetomo General Hospital starting from 2010 until 2015. Research population was all neuroblastoma patients. An exclusion criterion in this research was incomplete medical record.

Variables observed in this research were: Neuron Specific Enolase (NSE), Lactate Dehydrogenase (LDH), Fine Needle Aspiration Biopsy (FNAB), and Bone Marrow Aspiration (BMA). The collected data is processed using Microsoft Excel and grouped according to predetermined criteria, then described in the form of tables and narration.

RESULTS

There were 52 neuroblastoma patients from January 2010 until December 2015 period of time. Table 2 delivers information that most patients have high level of NSE examination with percentage of 56%, followed by 22 people (42%) that were not examined. Table 3 represents that LDH level of neuroblastoma patients were mostly found in less than normal category with percentage of 44%. While 19% of them had normal LDH level. Table 4 indicates that malignant round cell tumor had the highest frequency in FNAB examination from 52 patients, approximately 42%, whereas 37% of them did not undergo FNAB examination. Table 5 illustrates the result of Bone Marrow Aspiration (BMA) examination of patients with neuroblastoma. The result showed that most patients had a normocell formation (31%), had no cell nest (42%), had no rosette formation (48%), and did not shows elongated cytoplasm (48%). The final result showed that most patients (38%) were diagnosed with neuroblastoma.

| Variable     | Frequency (n) | Percentage (%) |
|--------------|---------------|----------------|
| Sex          |               |                |
| Male         | 29            | 56             |
| Female       | 23            | 44             |
| Age          |               |                |
| <1 years old | 4             | 8              |
| 1-5 years old| 37            | 71             |
| 5-10 years old| 10           | 19             |
| >10 years old| 1             | 2              |

Table 2. NSE Examination

| NSE                  | Frequency (n) | Percentage (%) |
|----------------------|---------------|----------------|
| Normal (<16)         | 1             | 2              |
| More than normal     | 29            | 56             |
| No description       | 19            | 37             |

Table 3. LDH Examination

| LDH                  | Frequency (n) | Percentage (%) |
|----------------------|---------------|----------------|
| Normal (313-618)     | 10            | 19             |
| Less than normal     | 23            | 44             |
| More than normal     | 0             | 0              |
| No description       | 19            | 37             |

Table 4. FNAB Examination

| FNAB                          | Frequency (n) | Percentage (%) |
|-------------------------------|---------------|----------------|
| Malignant round cell tumor    | 22            | 42             |
| Malignant tumor               | 3             | 6              |
| Metastasis neuroblastoma      | 3             | 6              |
| Malignant spindle mesenchymal | 1             | 2              |
| Metastasis retinoblastoma     | 2             | 4              |
| No evidence of malignancy     | 1             | 2              |
| Lymphoid immature atypic cells| 1             | 2              |
| No description                | 19            | 37             |

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DISCUSSION

The aim of the study was to investigate characteristic of tumor markers and pathological finding in neuroblastoma patient only by assessing medical record. Due to some incomplete data in the medical record, the data acquired were limited. From 52 neuroblastoma patients, it was found that 30 of them underwent NSE examination, 29 (56%) of 30 patients have increased serum NSE. NSE is an important marker in adult neuroendocrine tumors because neuroblastoma has certain neuroendocrine properties (7). Increase concentrations of serum NSE is widely used as a tumor marker to indicate poor prognosis of patients who have been diagnosed with neuroblastoma. However, this test is generally insensitive due to increasing serum NSE which is found on all neuroblastoma stage at diagnosis (1). Other research found that NSE had a correlation with tumor size at diagnosis (p < 0.001) and tumor related death (p < 0.01) in neuroblastoma. In neuroblastoma patients, particularly with advanced disease, chromogranin A (CgA) and NSE concentrations were elevated. Only NSE examination correlated to primary tumor size and outcome in neuroblastoma, even though both CgA and NSE correlated to genetic marker. That study concluded that CgA and NSE are clinically valuable tumor markers in neuroblastoma (7).

Clinical parameters such as stage at diagnosis of neuroblastoma, ferritin level, age of the patient, and LDH, determine the category of neuroblastoma, as well as prediction of the patient’s prognosis (8). In general, the level of tumor markers had good results to determine metastatic relapse or disease progression. NSE and LDH level were nearly equal in terms of sensitivity in the assessment of local recurrence, but to diagnose metastatic recurrence, NSE has a more sensitive value (9).

Other study conducted by Cangemi et al. (10) mentioned that in 279 patients, high LDH values positively associated with worse prognosis (P < 0.01) both in patients with localized and metastatic disease. Notably, patients with localized disease with LDH values > 1300 IU/mL had 12.9 times greater chance of relapse (95% CI: 3.34–49.78; P < 0.001)10. But in this study, most of the patient had lower level of LDH (n=23) and also had limitation because there were 19 (37%) patients without data of LDH examination. Normal or decreased level of LDH presumably caused as the consequent of chemotherapy. A study by Liu et al. (11) describes that 51 patients had decrement of serum LDH level after 2 months receiving chemotherapy among the 173 patients with malignancies, and obtained a prominent enhanced survival (11).

On FNAB examination, it was found that the majority of patients (42%) showed a malignant round cell tumor, this image may also appear on Ewing’s sarcoma, PNET, small cell osteosarcoma, mesenchymal chondrosarcoma, desmoplastic small round cell tumor, rhabdomyosarcoma, olfactory neuroblastoma, cutaneous neuroendocrine carcinoma, small cell melanoma, small cell carcinoma, and lymphoma (12). Thus, ensuring neuroblastoma with only FNAB examination is not enough.

BMA examination of neuroblastoma patients in this data showed that the majority of patients who came to the hospital were already experiencing metastatic neuroblastoma, with the discovery of cell nest in patients (33%), rosette formation (27%), and elongated cytoplasm (27%). A study in 1998 about BMA examination showed rosette formations appeared in 6 patients among 14 patients (13). Cell nest formation, rosette formation, and elongated cytoplasm were markers of metastasis in BMA examination. This research also found that there were 17 out of the 52 patients who had experienced the presence of these signs, showing a metastasis process with a percentage of 33%.

Table 5. BMA Examination

| Variable           | Frequency (n) | Percentage (%) |
|--------------------|---------------|----------------|
| Cell Formation     |               |                |
| Normocell          | 16            | 31             |
| Hipocell           | 9             | 17             |
| Hipercell          | 9             | 17             |
| Normohipocell      | 3             | 6              |
| Normohipercell     | 1             | 2              |
| No description     | 13            | 25             |
| Cell Nest          |               |                |
| (+)                | 15            | 33             |
| (-)                | 22            | 42             |
| No description     | 15            | 25             |
| Elongated cytoplasm|               |                |
| (+)                | 14            | 27             |
| (-)                | 25            | 48             |
| No description     | 13            | 25             |
| Rosette formation  |               |                |
| (+)                | 14            | 27             |
| (-)                | 25            | 48             |
| No description     | 13            | 25             |
| Conclusion         |               |                |
| Neuroblastoma      | 20            | 38             |
| Non diagnostic     | 16            | 31             |
| Hipoplastic marrow | 2             | 4              |
| ALL-L1             | 1             | 2              |
| No description     | 13            | 25             |
CONCLUSIONS

Based on tumor markers and pathological finding, this study revealed that the majority of neuroblastoma patients had poor prognosis. Specifically in BMA examination, majority of patients showed sign of metastasis process. Further studies with more complete data are therefore necessary to establish whether tumor markers and pathological findings are associated with cancer survival and prognosis of the patient, to further improve work-up treatment.

DECLARATION

Competing Interest
The author(s) declare no competing interest in this study

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