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NUTRITION STATUS AND NEUROPSYCHIATRIC DISORDERS IN INDONESIAN CHILDHOOD LUPUS: EXPERIENCE AT A SINGLE TERTIARY REFERRAL CENTER

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ABSTRACT

NPSLE diagnosis is still challenging because of many SLE-related and non-SLE-related processes that can be presented in patient. The report of NPSLE in Indonesia is still limited. This study aim to describe the clinical features, nutrition status, and laboratory characteristics of Neuropsychiatric Systemic Lupus Erythematosus (NPSLE) and compared to non NPSLE case in Indonesian children. The study is a retrospective cohort study. Data were collected from the complete medical record of Juvenile Systemic lupus Erythematosus (jSLE) patients 2016 - 2020 at the Allergy Immunology Outpatient clinic at Dr. Soetomo General Academic Hospital. We include all patients with ages ranging from age 0-18 years old with a diagnosis of Systemic lupus Erythematosus (SLE). The diagnosis fo SLE based on American College of Rheumatology (ACR) criteria 1997 and Neuropsychiatric (NP) manifestations were classified using the standardized nomenclature and case definitions for the 19 NP manifestations linked to SLE developed in 1999 by the ACR ad hoc Committee. Disease activity SLE was defined according to the American Mexican-Systemic Lupus Erythematosus Disease Activity Index (Mex-SLEDAI) criteria. Statistical analysis conducted in this study was descriptive analysis, paired T-test (NPSLE vs. non-NPSLE as the dependent variable), Fischer exact test, and Pearson Chi-square test using SPSS ver. 21. A total of 90 patients with juvenile SLE were enrolled, but only 71 patients were eligible as participants with complete medical records obtained. Mex-SLEDAI score was significantly higher on NPSLE compared to non-NPSLE ($p=0.001$). There are no significant differences of body height, body weight, and body mass index between each group ($p>0.05$). The incidence of NPSLE was 29.57%, with clinical main symptoms were delirium (33.33%), seizures (33.33%), and psychosis (14.29%). 33.33% MRI/CT-scan findings noted brain abnormalities with the most prevalent were ischemic (14.29%), hypodense lesion, brain atrophy, multiple lymphadenopathy, and transverse myelitis (4.76%). The higher disease activity in NP SLE indicates the needs to close observation, the higher patient adherence to medication, and more comprehensive management to achieve therapeutic success.

Keywords: juvenile, mortality, neuropsychiatry, SLE, symptoms

INTRODUCTION

Juvenile Systemic lupus Erythematosus (jSLE) involves a broad of organ manifestations, including nervous system manifestation, which is one of the major causes of morbidity and mortality. The involvement of nervous system manifests in the form of neuropsychiatric, known as Neuropsychiatric Systemic Lupus Erythematosus (NPSLE), with an incidence of approximately 20-45% in children with SLE (Harel et al., 2006; Yu et al., 2006). The incidence of NPSLE is common in juvenile SLE or childhood-onset, with clinical symptoms such as a decline in work memory, verbal memory, and speed processing which has negative effects on academic achievement, school attendance, and affected the quality of life (Zúñiga, 2014; Patrícia et al., 2019). The symptoms of NPSLE vary involving the central and peripheral nervous system, from diffuse Central Nervous System (CNS) disorders, such as acute confusion, psychosis, anxiety, and depressive disorders, to focal CNS syndromes, such as seizures, cerebrovascular disease, chorea, and myelopathy (Benseler and Silverman, 2007; Patrícia et al., 2019).

Nutrition status in SLE patients play a significant role in the occurrence of the symptoms. The body mass index determined quality of life as well. SLE patients with overweight and obese nutrition status reported to have higher possibility to experience fatigue and other symptoms (Zhu et al., 2010). Therefore it is important to have understanding between BMI and SLE in children.

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Until now, NPSLE diagnosis is still challenging because of many SLE-related and non-SLE-related processes that can be presented in patient. Several studies have reported the prevalence and clinical symptoms of NPSLE under the American College of Rheumatology (ACR) criteria (Harel et al., 2006; Yu et al., 2006; Benseler and Silverman, 2007; Costagliola et al., 2018). The report of NPSLE in Indonesia is still limited. Therefore we aim to investigate the involvement of neuropsychiatric manifestation in childhood-onset SLE or juvenile SLE in tertiary referral hospitals in Surabaya in order to increase the knowledge of NPSLE cases specifically in Indonesia. We describe the clinical features, nutrition status, and laboratory characteristics of Neuropsychiatric Systemic Lupus Erythematosus (NPSLE) and compared to non NPSLE case in Indonesian children.

METHODS

The study was a retrospective cohort which taking data from complete medical records of jSLE patients from allergy-immunology outpatient clinics and wards during 2016-2020 at Dr. Soetomo General Academic Hospital. The Health Research Ethics Committee of Dr. Soetomo Surabaya had approved the study (Ethical Clearance Number 0077/LOE/301.4.2/VII/2020). Patient less than 18 years old with complete data and fulfilled 4 of the 11 SLE criteria from the 1997 ACR were included in this study. Other causes of neurologic symptoms such as electrolyte disturbances, metabolic disorders, and infections were also excluded. Patients with NP manifestation prior to JSLE diagnosis of more than 6 months were also excluded from the analysis. Patient who experienced neuropsychiatric symptom more than 6 months prior to jSLE diagnosis were excluded from NPSLE case. Similarly, patients with only one neuropsychiatric symptom such as headache, mood disorder, or anxiety were not included in NPSLE cases as these are symptoms which often found in population and the most likely causes is not the SLE.

The data collected were demographic data including gender, age, age at first diagnosis, family history of autoimmunity, clinical symptoms, anthropometric measurement results, and laboratory-radiology results. While the criteria used for the diagnosis of SLE were the 1997 ACR criteria. Disease activity was measured using the Mex-SLEDAI, and NPSLE symptoms were classified based on the case definition by the ACR ad hoc committee (Guzman et al., 1992; Aviña-Zubieta et al., 2007). Examination of antinuclear antibodies (ANA) by immunofluorescence with the (4′,6-Diamidine-2′-phenylindole dihydrochloride) DAPI kit method and anti-dsDNA by enzyme-linked immunosorbent assay eBioscience kit (USA) were recorded.

Patients were divided into two groups, namely the non-NPSLE and NPSLE groups. Both group compared using statistical analysis include Levene's test and normality test, descriptive analysis, paired T-test (NPSLE vs. non-NPSLE as the dependent variable), Fischer exact test, and Pearson Chi-square test using SPSS version 21.

RESULTS AND DISCUSSIONS

A total of 71 patients were collected in this study and 21 people (29.57%) with NPSLE symptoms were found. Eleven out of 21 patients (52%) were diagnosed with NPSLE since their first admission to the hospital. The average age was 156.48 ± 25.82 months old or 13.03 ± 2.15 years old, the ratio between boys and girls was 13/58. The participant characteristics were summarized in Table 1.

This study found no significant difference on age (156.48 ± 25.82 months old vs. 143.76 ± 43.87 months old, p=0.220), body weight (39.09 ± 9.81 kg vs. 34.14 ± 13.71 kg, p=0.161), body height (143.21 ± 8.87 cm vs. 139.07 ± 22.88 cm, p=0.429), body mass index (17.82 ± 7.45 kg/cm^2 vs. 16.98 ± 1.28 kg/cm^2, p=0.748), duration of the symptoms (186.65 ± 499.38 days vs. 71.50 ± 84.60 days, p=0.140), C3 (62.75 ± 36.09 units vs. 52.89 ± 37.67 units, p=0.314), ANA test (181.68 ± 161.69 units vs. 193.21 ± 140.68 units, p=0.772) and anti dsDNA (418.21 ± 350.58 units vs. 527.81 ± 562.55 units, p=0.437), hemoglobin (9.28 ± 3.35 mg/dL vs. 10.90 ± 11.43 mg/dL, p=0.528), white blood cells (476.00 ± 7,408.68/mm^3 vs. 6,830.00 ± 2,990.80/mm^3, p=0.184) and platelet (284,380.95 ± 193,571.81/mm^3 vs. 226,719.80 ± 126,975.94/mm^3, p=0.142). Only the Mex-SLEDAI score

showed a significant difference between NPSLE with non-NPSLE (11.28 ± 4.36 vs. 6.68 ± 3.53, p<0.001).

There was no significant difference in the gender distribution of both groups (p=0.319). Boys to girls ratio was 2:19 on NPSLE and 11:29 on the non-NPSLE group. The most frequent symptoms of NPSLE were fever (42.86%) followed by rash (14.29%), pale and joint or bone pain (9.53%). Swollen, dizziness, and seizure only account for 4.76%. While on non-NPSLE participants, the most frequent symptom was rash (26%), fever 22%, pale (20%), joint or bone pain (10%), swollen (6%), bleeding, and rash (4%). Other symptoms, icterus, personality changes, fever, seizures, and rash and ulcer account for 2%. There is no significant difference in the main complaint incidence in both groups (p=0.252). Also, we found no significant difference in the disease outcome (p=0.397).

The clinical symptoms and MRI/CT-scan findings of NPSLE were summarized in Table 2. The most prevalent clinical symptoms of NPSLE were delirium (33.33%), seizures (33.33%), and psychosis (14.29%). While Parkinson's, dizziness, depression, and eye problems account for 9.52%. Vasculitis, paraplegia, epilepsy, and sleep disorders incidence was 4.76%.

Not all patients undergo CT scans and MRI/CT-scan. The abnormalities were detected in 7 (33.33%) subjects with NPSLE. The most frequent was ischaemic (14.29%), such as a hypodense lesion, brain atrophy, multiple lymphadenopathies, and transverse myelitis incidence was found in 1 patient (4.76%). Thirty-eight percent of NPSLE children had normal Magnetic Resonance Imaging (MRI) or Computed Tomography Scan (CT-scan) results.

Table 1. Subject Characteristics

Characteristic	NPSLE (n=21)	Non-NPSLE (n=50)	p
Age, month (mean ± SD)	156.48 ± 25.82	143.76 ± 43.87	0.220
Gender, (n (%))			0.319
- Boys	2 (9.53)	11 (22)	
- Girls	19 (90.47)	39 (78)	
Body weight, kg (mean ± SD)	39.09 ± 9.81	34.14 ± 13.71	0.161
Body Height, cm (mean ± SD)	143.21 ± 8.87	139.07 ± 22.88	0.429
Body Mass Index, kg/cm^2 (mean ± SD)	17.82 ± 7.45	16.98 ± 1.28	0.748
Complaints, (n (%))			0.252
- Fever	9 (42.86)	11 (22.00)	
- Pale	2 (9.53)	10 (20.00)	
- Swollen	1 (4.76)	3 (6.00)	
- Dizziness	1 (4.76)	0 (0.00)	
- Bleeding	0 (0.00)	2 (4.00)	
- Rash	3 (14.29)	13 (26.00)	
- Seizure	1 (4.76)	0 (0.00)	
- Joint/bone pain	2 (9.53)	5 (10.00)	
- Breathless	0 (0.00)	2 (4.00)	
- Icterus	0 (0.00)	1 (2.00)	
- Personality changes	0 (0.00)	1 (2.00)	
- Fever, seizure	0 (0.00)	1 (2.00)	
- Pale, joint or bone pain	1 (4.76)	0 (0.00)	
- Rash, ulcer	0 (0.00)	1 (2.00)	
- Swollen, seizure	1 (4.76)	0 (0.00)	
Duration of the symptoms, days (mean ± SD)	186.65 ± 499.38	71.50 ± 84.60	0.140
C3, unit (mean ± SD)	62.75 ± 36.09	52.89 ± 37.67	0.314
ANA Test, unit (mean ± SD)	181.68 ± 161.69	193.21 ± 140.68	0.772
Anti-dsDNA, unit (mean ± SD)	418.21 ± 350.58	527.81 ± 562.55	0.437

Characteristic	NPSLE (n=21)	Non-NPSLE (n=50)	p
Hemoglobin (HB), mg/dL (mean ± SD)	9.28 ± 3.35	10.90 ± 11.43	0.528
White Blood Cells (WBC), /mm^3 (mean ± SD)	8,476.00 ± 7,408.68	6,830.00 ± 2,990.80	0.184
Platelet, /mm^3 (mean ± SD)	284,380.95 ± 193,571.81	226,719.80 ± 126,975.94	0.142
MEX SLEDAI Score	11.28 ± 4.36	6.68 ± 3.53	0.001
Anemia, (n (%))	15 (71.43)	43 (86.00)	0.184
Leucopenia, (n (%))	7 (33.33)	10 (20.00)	0.240
Thrombocytopenia, (n (%))	2 (9.52)	6 (12.00)	1.000
Outcomes, (n (%))			0.397
- Remission	11 (52.38)	23 (46.00)	
- Death	7 (33.33)	5 (10.00)	
- Lupus nephritis complication	2 (9.52)	10 (20.00)	
- Other complication	1 (4.76)	2 (4.00)	
- Loss of follow-up	0 (0.00)	10 (20.00)	

In this study, there are no significant differences in nutritional status between NPSLE and non-NPSLE. But if we see to the category of the BMI, most of the patients are included as underweight, with BMI less than 25 kg/m^2. SLE patients with active disease are mostly have rapid and severe weight loss which then lead to undernutrition. Study in Brazil showed 70.1% patients with autoimmune disease are undernutrition (Waitzberg, Caiaffa and Correia, 2001). In the case of SLE, there are still no well understanding of the factors which resulting to undernutrition, because it can be coming from genetic, environmental, and hormonal factors (Pocovi-Gerardino et al., 2018; Correa-Rodríguez et al., 2019). But, it is important to study about the quality of diet because it may impact to the undernutrition status in patients, which then resulting to a more severe condition namely anemia, low bone mineral density, cardiovascular diseases, and many more (Borges et al., 2012; Ahn et al., 2018).

Several studies have been conducted to investigate the incidence of NPSLE, with varied results, ranging from 2% to 95%, which was similar to this result (Yu et al., 2006; Benseler and Silverman, 2007; Muscal and Brey, 2010; Giani et al., 2021). Central Nervous System (CNS) is the most affected compared to the peripheral and autonomic nervous system (Harel et al., 2006; Benseler and Silverman, 2007) and more severe in children patients compared to adult patients, which is the major causes of mortality and morbidity, such as resulting in organ damage with poor prognosis (Jeltsch-david and Muller, 2014; Khajezadeh et al., 2018). The impact counted for more than 90% of NPSLE cases (Kivity et al., 2015; Sassi et al., 2017). Many factors contribute to the inconsistency of the incidence of NPSLE, including the study design, study methodology, selection criteria, and the scarcity of several neuropsychiatric syndrome (Jeltsch-david and Muller, 2014).

The causes of NPSLE are still unclear, but it is suggested that antibody-mediated neurotoxicity, vasculopathy due to anti-phospholipid (aPL) antibodies and cytokine-induced neurotoxicity, and the loss of neuroplasticity are the highest possible causes, which affected directly to gray and white matter structures (Muscal et al., 2010; Kivity et al., 2015). The pathological mechanism of NPSLE started by a subset of cross-reactive anti-double-stranded deoxyribonucleic acid (DNA) autoantibodies binding to NR2 glutamate receptor, which then triggered neuronal death due to glutamate release and excitatory cell death (Muscal and Brey, 2010). Neuropsychiatric manifestation of SLE was associated with the disease activity, which is in line with these findings (Yoon et al., 2019). Mex-SLEDAI score was significantly higher in NPSLE. Others found that NPSLE participants suffered from organ damage at a higher rate (The Systemic Lupus International Collaborating Clinics (SLICC) / ACR Damage Index), compared to non-NPSLE (Jo et al., 2002). Anti-glutamate receptor antibodies may also play a role in cognitive dysfunction and psychiatric disease in patients with SLE. Degiorgio first demonstrated that a subset of lupus anti-DNA antibodies cross-react with the NR2 glutamate receptor in patients with SLE (Degiorgio et al., 2001).

Table 2. Clinical symptoms

Clinical symptoms	n (%)	MRI/CT-scan	n (%)
Parkinson	2 (9.52)	Hypodense lesion	1 (4.76)
Moody	2 (9.52)	Brain atrophy	1 (4.76)
Delirium	7 (33.33)	Multiple lymphadenopathies	1 (4.76)
Seizure	7 (33.33)	Ischaemic	3 (14.29)
Dizzy	2 (9.52)	Transverse myelitis	1 (4.76)
Vasculitis	1 (4.76)	Normal MRI/CT-Scan	8 (38.10)
Psychosis	3 (14.29)	Not enrolled	6 (28.57)
Paraplegia	1 (4.76)		
Epilepsy	1 (4.76)		
Sleep disorders	1 (4.76)		
Depression	2 (9.52)		
Eye problems	2 (9.52)		
No symptoms	3 (14.29)		

The onset of NPSLE in the previous study varies from 12 – 15.2 years old (Carolyn, Doughty and Athreya, 1981; Harel et al., 2006; Yu et al., 2006; Costagliola et al., 2018). A study conducted in Bangkok noted the onset of NPSLE was started from 13 years old which was similar to this study (Suwanpakdee and Hostpital, 2017). Several studies noted the onset of SLE around the age of 16 to 55 years old, or childbearing age. Many factors are involved in the etiology and pathogenesis of SLE, including hormonal change (Sassi et al., 2017). It was proposed that hormonal changes, including steroid sex, which might be constituted of an endogenous milieu that promotes the development of SLE in a susceptible individual, accompanied by environmental factors (Jeltsch-david and Muller, 2014).

The most frequent symptoms of the study were seizure and delirium, which is in line with other findings (Khajezadeh et al., 2018). The incidence of seizure was 7-30% of NPSLE participants as the mark of the earliest CNS manifestation and focal CNS syndromes (Jeltsch-david and Muller, 2014; Salman-monte, Monfort and Carri, 2021). But previous study stated the incidence of seizures was more than 40% (Harel et al., 2006; Yu et al., 2006). Generalized, seizures tend to be associated with disease activity, and it was important to exclude the causes of seizures (Kivity et al., 2015). Seizures are slightly more prevalent at the onset and during disease in childhood SLE compared to adult SLE (Salman-monte, Monfort and Carri, 2021). Delirium or "acute confusional state", known as Lupus cerebritis, has an incidence ranging from 0 to 7%, which is much lower than this study, which suggest the involvement of primary CNS with the disease (Turkel, Miller and Reiff, 2001; Kivity et al., 2015). A study in Malaysia counted the incidence of delirium as 24.2%, and 26% in China, which was lower than this study (Fan et al., 2014).

Psychosis was the primary manifestation of SLE and part of the criteria for "neurologic disorder", and mostly present due to corticosteroids medication (immunosuppressive therapy) and active lupus, especially if the dose is high, so it is important to distinguish the cause of psychosis by reducing the dose of corticosteroids and monitoring lupus activity, which it affects 2-11% of the patients (Turkel, Miller and Reiff, 2001; Mak et al., 2008; Kivity et al., 2015). The other studies showed that the incidence of psychosis was 18.5-24.2% which was higher than this study (Saunders et al., 2016). It also indicates active CNS disease in approximately 60% of cases (Turkel, Miller and Reiff, 2001).

NPSLE is complicated and difficult to diagnose due to the variation of neurologic manifestations and confounding disorders, so that brain imaging is important to determine the diagnosis (Jr et al., 2010). Anatomical cerebral abnormalities were found in 25% of SLE patients (Sibbitt, Sibbitt and Brooks, 1999). The incidence of abnormal MRI varies between 19-75% in

NPSLE (Jeong et al., 2015). MRI/CT-scan with no abnormal findings in NPSLE was 59% which is much higher than this study (38.10%) (Saunders et al., 2016). However, it has been noted that the incidence of normal brain MRI in SLE ranged between 34 - 41% (Cannerfelt, Nystedt and Jo, 2018). An abnormal finding was found in 33% of adult NPSLE, which is similar to this study (Steinlin et al., 1995).

Ischemic was predominant in this study, it happened in 16.7% of adult NPSLE, which was similar to this study (Zaky et al., 2015). Ischemic might be mediated by the overproduction of pro-inflammatory cytokines which damaging the brain-blood barrier (BBB) in different sites, and further, representing various neuropsychiatric symptoms because auto-antibody entering the brain. Pro-inflammatory responses by monocytes or endothelial cells might be induced by Anti-ribosomal-P and anti-NR2 antibodies (Kivity et al., 2015). Due to the high incidence of ischemic, SLE is an independent risk factor for stroke, which the incidence was 15%. It was noted that patient aged more than 50 years old had a higher risk of stroke, 1.5-fold in the first 5 years of the disease (Sibbitt, Sibbitt and Brooks, 1999).

MRI examination showed brain lesion in NPSLE patients (Sibbitt, Sibbitt and Brooks, 1999). It was stated that the reduction of N-acetyl aspartic acid (NAA) in NPSLE correlates with small focal lesions elsewhere in the brain as seen on MRI. The reduction of NAA is also seen in patients with generalized seizures, psychosis, or delirium. Low levels of NAA due to cytotoxic effects (e.g. antineuronal antibodies, cytokines, or small molecule neurocytotoxins) (Jr et al., 2010). Hypodense lesion happened to 1 (4.76%) NPSLE participant.

The incidence of brain atrophy occurs in 8.7 to 32% of patients with SLE, the incidence of brain atrophy in this study was still in this range (Zaky et al., 2015). Other stated higher incidence of brain atrophy in NPSLE patients, ranging from 19–43% (Cannerfelt, Nystedt and Jo, 2018). It is the most common finding in NPSLE (Cannerfelt, Nystedt and Jo, 2018; Silvagni et al., 2022). The disruption of BBB might be the most common cause of dysfunction of the blood-cerebrospinal fluid barrier and causing brain atrophy due to the loss of parenchymal structures (Silvagni et al., 2022). White matter lesions and brain atrophy have correlation to cognitive dysfunction, but the specific domain has not been specified (Cannerfelt, Nystedt and Jo, 2018). Atrophy developed slowly over several years, and involved the frontotemporal regions (gray and white matter). It is correlated with the disease activity and the duration of the disease, complement deficiency, aPL antibodies, and the duration of corticosteroid treatment (Sarbu and Sarbu, 2020).

Lymph nodes are the peripheral organs. Brain tissue reactive antibodies are synthesized in the CNS and peripheral organs, including lymph nodes, and crossing the BBB, which was affecting the neurons (Magro-checa, Steup-beekman and Huizinga, 2018). The prevalence of lymphadenopathy in SLE is still unknown, although several cases report that generalized lymphadenopathy is the manifestation of SLE (Magro-checa, Steup-beekman and Huizinga, 2018). This study found the incidence of lymphadenopathy in 1 subject. The incidence of myelopathy was rare in SLE with severe effects which estimated a prevalence of 1%. Acute transverse myelitis is caused by an inflammatory process (Monahan et al., 2020). Our study found 1 subject with transverse myelitis, with rapid onset of motor, sensory and autonomic dysfunction at a spinal cord level.

CONCLUSION

This study found no significant difference on age, body weight, body height, body mass index, duration of the symptoms, C3, ANA test and anti dsDNA, hemoglobin, white blood cells and platelet ($p>0.05$). Only the Mex-SLEDAI score showed a significant difference between NPSLE with non-NPSLE ($p<0.001$). NPSLE in Indonesian children is quite rare with varied clinical manifestations. The higher disease activity in NP SLE indicates the need for close observation, higher patient adherence to medication, and more comprehensive management to achieve therapeutic success.

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