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Profile of Neuropsychiatric Manifestations in Pediatric Systemic Lupus Erythematosus (SLE) Patients

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ABSTRACT

Background: Systemic Lupus Erythematosus (SLE) is a systemic autoimmune disease involving multiple systems and is associated with significant morbidity and mortality. SLE can cause serious organ damage, one of which is the nervous system, known as neuropsychiatric SLE (NPSLE). Neuropsychiatric manifestations affect nearly half of SLE patients; the impact is very large on the severity of the disease, quality of life, and the prognosis of SLE. The symptoms vary from being diffuse and mild to causing acute life-threatening events. ***Objective:*** This study aimed to analyze the profile of neuropsychiatric manifestations of pediatric patients with SLE at Dr. Soetomo General Academic Hospital Surabaya for the period of January 2023–June 2024. ***Methods:*** This is a retrospective observational descriptive study design based on secondary data from Dr. Soetomo General Academic Hospital Surabaya. The study objects were 38 pediatric SLE patients whose ages were below 18 years old. The variables of this study were age, sex, and neuropsychiatric manifestation. ***Result:*** From 38 pediatric SLE patients, there were 18 patients (47.4%) with neuropsychiatric manifestations. From those 18 patients, the most common neuropsychiatric manifestations were cognitive dysfunction (38.9%), headache (33.3%), and mood disorders (27.9%).

Keywords: systemic lupus erythematosus (SLE); pediatric; neuropsychiatric manifestations; lupus; neuropsychiatric systemic lupus erythematosus (NPSLE).

INTRODUCTION

Systemic Lupus Erythematosus (SLE) is a systemic autoimmune disease that occurs multi-systemically and is associated with significant levels of morbidity and mortality [1]. In this disease, the immune system will lose its ability to differentiate foreign substances from the body's cells or tissues. The body produces autoantibodies, namely excessive antibodies that do not attack germs or antigens, but the body's immune system cells and tissues [2]. According to the Indonesian Health Minister in 2022, SLE is known as "the disease of a thousand faces", since each patient has different clinical manifestations and is often similar to other diseases [3]. SLE patients have some phenotypes with clinical presentations that vary, from mild mucocutaneous manifestation to severe damage of multiple organs, such as the central nervous system [1].

Neuropsychiatric (NP) manifestations affect nearly half of SLE patients, therefore the impact is very large on the severity, quality of life, and prognosis of SLE patients [4]. From a cross-sectional study using medical records in Surabaya, Indonesia in the period of January–December 2017, neurological disorder is the third most common manifestation after hematological disorder and arthritis in SLE patients [5]. Manifestation of neurological symptoms in SLE patients varies from the diffuse and mild ones to those that cause acute life-threatening events [4].

It is estimated that 25% of children with SLE experience neuropsychiatric manifestations (NP) due to SLE, which is a major cause of morbidity and mortality in SLE patients. NP manifestations may be the initial presentation of SLE in children where mortality rates are relatively low, but morbidity can be significant and may cause permanent damage [6].

The pathophysiology of the neuropsychiatric Systemic Lupus Erythematosus (NPSLE) mechanism still remains poorly understood. There are several risk factors found to be the potential cause of NPSLE pathogenesis, which are the autoimmunity or inflammation pathway and the thrombotic or ischemic pathway [7]. NPSLE is defined as neurological and psychiatric syndromes that involve central, peripheral, and autonomic nervous system in SLE patients after the other causes are ruled out [5].

Primary NPSLE includes the NPSLE because of inflammation and ischemic, while secondary NPSLE may occur due to organ damage because of SLE or SLE therapy [7].

The American College of Rheumatology (ACR) in 1999 released a classification in diagnosing NPSLE which covers 12 manifestations of the central nervous system and 7 manifestations of the peripheral nervous system [5]. SLE itself can cause severe organ damage, one of which is the central nervous system, besides the kidney [8]. This study aims to assess the profile of neuropsychiatric manifestations in pediatric SLE patients at Dr. Soetomo General Academic Hospital, with the aim of helping physicians to know the NP manifestations as clinical signs of SLE in pediatric patients.

METHODS

This was a retrospective observational descriptive study using secondary data. The secondary data used were from the medical records of pediatric patients who were diagnosed with Systemic Lupus Erythematosus (SLE) at Dr. Soetomo General Academic Hospital Surabaya during the period of January 2023–June 2024. The variables in this study contain the patient's general characteristics, which are the range of age, sex, and neuropsychiatric manifestations. The method used is a total sampling technique, taking all subjects who fulfilled the inclusion criteria, namely patients who had complete medical records, including name, age, diagnosis, and complaints. A patient who had an incomplete medical record was excluded.

RESULTS AND DISCUSSION

The total number of cases of patients who were diagnosed with Systemic Lupus Erythematosus (SLE) at the Pediatric Department of Dr. Soetomo General Academic Hospital Surabaya during the period of January 2023–June 2024 was 38 cases. Of those 38 patients, there were 18 patients (47.37%) experienced neuropsychiatric symptoms.

TABLE 1: The Frequency Distribution of the Presence of Neuropsychiatric Manifestations in Pediatric SLE Patients.

The Presence of Neuropsychiatric Manifestation	Frequency (n)	Percentage (%)
Yes	18	47.37
No	20	52.63
Total	**38**	**100**

The results of this research are aligned with the review by [4], which neuropsychiatric (NP) manifestations affect nearly half of SLE patients, and the impact is very large on the severity, quality of life, and prognosis of SLE patients. In a study in the UK, 25% of juvenile SLE patients exhibited NP manifestations, and half of them were at the first visit [9]. Most childhood-onset SLE patients encounter NP manifestations in the first 2 years of the disease, with 30-70% of patients present with more than one NP event [10]. A systematic review and meta-analysis investigating SLE patients in Pakistan showed that the prevalence of the disorders regarding neuropsychiatry was estimated to be 30.42% [11]. A study aiming to analyze the clinical and immunological features of pediatric-onset SLE and NPSLE stated the data of NP manifestations in the Spanish pediatric population is rare, meanwhile, the prevalence of the manifestations varied from 29% to 44% in different series [12].

Based on Table 2, it showed that in the period of January 2023–June 2024 at Dr. Soetomo General Academic Hospital Surabaya, the incidence of neuropsychiatric manifestations occurred in 17 females (94.44%) and 1 male (5.56%). Needed to be discovered, the data that were obtained in this research by total sampling technique in a period of January 2023–June 2024 at Dr. Soetomo General Academic Hospital Surabaya, from 38 total pediatric SLE patients, there were 35 females (92.11%) and 3 males (7.89%).

TABLE 2: Sex Distribution of Pediatric SLE Patients Who Experienced Neuropsychiatric Manifestations.

Sex (Gender)	Frequency (n)	Percentage (%)
Female	17	94.44
Male	1	5.56
Total	**18**	**100%**

The results are in line with the general prevalence of SLE patients that are dominated by females [2], [13]. The ratio of female lupus patients compared to males is 15:1 to 22:1 [13]. If compared to males, females tend to have stronger immune responses and are more susceptible to autoimmune diseases including SLE [14]. According to the Indonesian Health Minister, most lupus patients are females in their reproductive age [2]. Gender bias in SLE contributes to sex hormone activity, and some genes that are in the X chromosome [15]. SLE onset usually occurs in females in their age of childbearing, and becomes less common after menopause, indicating that estrogen plays a role in the disease [16]. Despite affecting females far greater than males, however, male patients' disease tends to be more severe than females [17]. It is estimated that 80% of pediatric patients are female, the same as adult SLE [18]. In this research, 17 of 35 (48.57%) female pediatric SLE patients experienced neuropsychiatric (NP) manifestations; and 1 of 3 (33.33%) male pediatric SLE patients encountered NP manifestations.

Based on Table 3, from demographic data of the pediatric SLE patients who exhibited NP manifestations, the most dominant age of SLE diagnosis distribution was among 10-<18 years old, which classified as teenagers as much as 17 of 18 patients (94.44%). There was 1 from 18 patients who were in the age of 5-<10 years old (5.56%). The age distribution used in this research was based on the Indonesian Health Minister in 2023 that classified age: 0-<5 years old (toddlers), 5-<10 years old (children), and 10-<18 years old (teenagers).

TABLE 3: Age Distribution of Pediatric SLE Patients Who Experienced Neuropsychiatric Manifestations.

Age Distribution	Label	Frequency (n)	Percentage (%)
0-<5 years	Toddlers	0	0
5-<10 years	Children	1	5.56
10-<18 years	Teenagers	17	94.44
Total		**18**	**100**

The results of this research were aligned with some studies that showed the median age of the onset of SLE in children was at the age of 11-12 years old [18]. Lupus incidence reaches its peak at the reproductive age of females, where SLE in females occurs in the range of 15 to 44 years of age [19]. It is only 20% of patients with SLE are diagnosed within the first two decades of their lives, and SLE is a very rare disease experienced by a child under 5 years of age [20]. The youngest age of a patient ever recorded with SLE was a 6-month-old girl in Latin America who clearly exhibited 4 criteria of SLE [21].

Based on Table 4, there are 18 pediatric SLE patients who experienced neuropsychiatric (NP) manifestations during the period of January 2023 to June 2024 at Dr. Soetomo General Academic Hospital Surabaya. Of those 18 patients, some of them experienced more than one criterion of NP manifestations.

TABLE 4: Profile of Neuropsychiatric Manifestations in Pediatric SLE Patients According to ACR, 1999.

Neuropsychiatric Manifestation	Frequency (n)	Percentage (%)
Neurological and focal syndrome		
Central Nervous System		
Aseptic meningitis	-	-
Cerebrovascular disease	1	5.56
Demyelinating Syndrome	-	-
Headache	6	33.33
Movement disorder	2	11.11
Myelopathy	-	-
Seizures	1	5.56
Peripheral Nervous System		
Polyneuropathy	-	-
Plexopathy	-	-
Gullain Barré syndrome	-	-
Autonomic disorders	-	-
Myasthenia gravis	-	-
Cranial neuropathy	-	-
Psychiatric and diffuse syndrome		
Acute confessional state	-	-
Anxiety disorder	3	16.67
Cognitive dysfunction	7	38.89
Mood disorder	5	27.78
Psychosis	-	-
Total	**18**	**100**

In this research, the highest incidence of NP manifestations is cognitive dysfunction, namely as many as 7 of 18 patients (38.89%). Cognitive dysfunction that occurred in SLE patients in this research was classified as slow learners with IQ between 90-70 and/or patients with other problems related to education and literacy. A retrospective study, [22], did an observation of clinical, laboratory, and radiographic features of SLE patients who were diagnosed under 18 years, showing the most common NP manifestation was cognitive dysfunction, followed by significant headache, seizure, psychosis, and focal neurological signs. In the Children's Hospital of Philadelphia, using the Wechsler Intelligence test, 13 of 37 children with SLE have an average IQ of 89 [23]. In research that compared children with SLE diagnosis and other healthy children that became control, lower social competency was found in children with SLE (P=0.03), however, the internal, external, and total behavior scores from those two groups did not show significant differences [24]. Education background also describes one's perspective about a disease and usually is related to NPSLE, especially cognitive function [25].

The second most common NP manifestation in this research was headache, in as many as 6 of 18 patients (33.33%). A retrospective study in 2014 exhibited that headache was the most frequent NP manifestation, 72.5% of NP manifestations that were experienced were headaches according to ACR, 1999 criteria [26]. The result of this research is also similar to a study in Bandung in the central nervous system manifestation that dominates SLE patients was headache [25]. Several studies showed that SLE-related headache is caused by idiopathic intracranial hypertension, and steroids should become the first-line therapy [27].

In this research, the finding of mood disorders was experienced by 27.78% of patients. The mood disorders in this research include organic mood disorders, mild depressive episodes, and moderate depressive episodes. In one systematic review, in patients with childhood-onset SLE, the prevalence of depressive symptoms varies from 6.7% to 59%, [28]. Depression itself can be an important cause of compliance problems in the consumption of medication [29]. It may be concluded that depressive symptoms are a common comorbidity that occurs in childhood-onset SLE [28]. Identifying SLE patients at risk for adherence problems, including depression, can improve treatment outcomes [29].

Based on this research, anxiety disorders were experienced by 16.7% of pediatric SLE patients exhibiting NP manifestations. The disorders include adjustment disorders and other types of anxiety disorders. In a study examining psychiatric manifestations in pediatric SLE patients, the most common psychiatric manifestations were anxiety disorders (52.6%) adjustment disorders, and depression (36.8% each) [30]. A study at Dr. Soetomo General Academic Hospital Surabaya in 2020, mentioned that mental health problems, including anxiety and depression, reduce the quality of life of

children with lupus nephritis, with the level of quality of life in the induction phase lower than the maintenance phase [31]. Manifestations of psychiatry are common in SLE patients with a prevalence of 17% to 75%, with the possible factors of mechanisms are vascular injury and the presence of pathogenic antibodies [32].

In this study, it was found that there were 11.1% of pediatric NPSLE patients had movement disorders or chorea, including hands that often have tremors or patients with involuntary limb movements. In one study, NPSLE was found in 51.85% of patients with SLE, while in contrast, the prevalence of chorea is rather high namely 6% of their SLE patients [33]. In a case report, there are SLE patients with acute movement disorders, that have several possible causes including vascular, infectious, metabolic, toxic causes, or autoimmune, where the most likely from the patient's age, clinical presentation, and laboratory examination, autoimmune is the origin of the movement disorder [34].

In this research, seizures also occurred in 5.6% of patients. In Iran, a study found that the most frequent NP manifestation in juvenile-onset SLE patients was headache (13%), followed by seizures (9.5%) and chorea (3.4%) [35]. The prevalence of seizures in SLE patients has a wide range from 2% to 8% [36]. The incidence of NPSLE can vary from global cerebral dysfunction to paralysis and seizures to mild and focal symptoms, such as headaches or memory disappearance [37]. Pathogenesis of seizures in SLE patients is the induction of ischemic stroke due to blood vessel deposition and occlusion, and the second is related to non-ischemic mechanisms, and increased neuronal excitability. Appropriate therapy is based on accurate diagnosis and identification of the risk of seizure occurrence, because recurrent seizures can change the comorbidity of SLE patients with seizures, reducing the seizure occurrence in autoimmune disease [36].

In this study, cerebrovascular disease was experienced by 5.6% of pediatric NPSLE patients. The main complaint was weakness in both legs, the patient was given an additional diagnosis of tetraplegia. In contrast to a retrospective study in Saudi Arabia, there was found 35% of SLE patients with stroke [38]. This difference may be due to the duration of the disease observed, in [38], the data was taken from the hospital from the period of 1 January 2000 to 31 May 2012. Cerebrovascular disease in juvenile-onset SLE (5.3%-39%) is associated with various cerebral vascular abnormalities, from vasculitis has an impact on small, medium, and large arteries, up to cerebral vein thrombosis [35]. Cerebrovascular events represent one of the most frequent and severe NP manifestations in SLE patients, with the prevalence of stroke in SLE varying from as little as 2% to as high as 19%, with an incidence that also varies, from 5.8 to 25.3 cases per 1,000 people every year [39].

In this study, it was found that NP manifestations existed in the central nervous system more than in the peripheral nervous system. This is in accordance with a prospective analysis, namely the incidence of NP having an impact on the central nervous system of 93.1% while those involving the peripheral nervous system were 6.9% [40].

CONCLUSIONS

From 38 pediatric SLE patients at Dr. Soetomo General Academic Hospital Surabaya in the period of January 2023 to June 2024, there were 18 patients (47.4%) with neuropsychiatric manifestations. From those 18 patients, the most common neuropsychiatric manifestations were cognitive dysfunction as much as 38.9%, headache with an incidence of 33.3%, and mood disorders was 27.78%. The other NP manifestations that occurred were anxiety disorders, chorea, seizures, and cerebrovascular disease.

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