PSYCHIATRIC MANIFESTATIONS IN PEDIATRIC SLE PATIENTS AT SIRIRAJ HOSPITAL BANGKOK, THAILAND

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Abstract. Although psychiatric manifestations in children with systemic lupus erythematosus (SLE) are common, published research on this topic is scarce. The aim of this study was to describe psychiatric manifestations in pediatric SLE patients including neuropsychiatric systemic lupus erythematosus (NPSLE) and associated factors. The retrospective chart review was performed among 34 pediatric SLE patients who received psychiatric consultation at Siriraj Hospital during the 2003 to 2012 study period. The results showed common psychiatric symptoms including mood change, anxiety, behavioral change, and cognitive dysfunction. Sixteen children had NPSLE and 18 patients had psychiatric symptoms not related to NPSLE. All children without NPSLE recovered from their psychiatric symptoms, whereas two children with NPSLE died. Factors found to be significantly associated with the diagnosis of NPSLE included presenting symptoms with more than one organ involvement, nervous system involvement, and cognitive dysfunction. In conclusion, this study highlights the importance of careful assessment and appropriate treatment of psychiatric manifestations, particularly NPSLE that indicates a less favorable prognosis and requires treatment with anti-inflammatory medications.

Keywords: psychiatric manifestations, pediatric SLE, neuropsychiatric SLE, NPSLE

INTRODUCTION

Systemic lupus erythematosus (SLE) is a chronic autoimmune disease that can cause inflammatory response in many organ systems of the body, including the nervous system (Levy and Kamphuis, 2012). Neuropsychiatric systemic lupus erythematosus (NPSLE) or nervous system involvement in SLE can present with a wide range of neurological and psychiatric symptoms (Fernandes and Brito, 2012). In pediatric SLE patients, NPSLE is an important cause of morbidity and mortality (Benseler and Silverman, 2007). Prevalence of NPSLE in pediatric SLE patients has been reported to be in the range of 22-95%, which appears to be higher than in adult SLE patients (Muscal and Brey, 2010).

The American College of Rheumatology (ACR) classifies NPSLE into nineteen neurological and psychiatric syndromes. The psychiatric syndromes include acute confusion state, anxiety disorder, mood disorder, and psychosis (1999). These psychiatric syndromes are defined according to the Diagnostic and Statistical Manual of Mental Disorders, 4th edition text revision (DSM-IV-TR) as delirium, anxiety disorder due to a medical disorder (SLE), mood disorder due to a medical disorder (SLE), and psychotic disorder due to a medical disorder (SLE), respectively (American Psychiatric Association, 2000). The pathophysi-

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ologic mechanisms of neurological involvement in these neuropsychiatric syndromes may include angiopathy, autoantibodies, inflammatory mediators, and atherosclerosis (Muscal and Brey, 2010). In addition to psychiatric manifestations that result from NPSLE, pediatric SLE patients may also present with psychiatric symptoms due to other causes, including psychological reactions to illness, primary psychiatric illnesses, and medication side effects (Beckerman *et al*, 2011; Kohut *et al*, 2013).

Few studies have been conducted in NPSLE among pediatric patients. Some studies have described neuropsychiatric symptoms in NPSLE, but most of those did not focus on the specific features of psychiatric manifestations (Olfat *et al*, 2004; Yu *et al*, 2006; Benseler and Silverman, 2007; Singh *et al*, 2009). Two studies described only psychiatric symptoms and one study described psychosis, depression, and cognitive dysfunction as the manifestations of NPSLE (Muscal *et al*, 2010; Lim *et al*, 2013; Alpert *et al*, 2014). However and according to our review of the literature, no studies have described psychiatric manifestations resulting from conditions other than NPSLE in pediatric SLE patients. The objective of this study was to describe psychiatric manifestations resulting from NPSLE and from other conditions in pediatric SLE patients who received psychiatric consultation at Siriraj Hospital. Our secondary objective was to assess factors associated with the diagnosis of NPSLE, as compared to the diagnosis of conditions not related to NPSLE.

MATERIALS AND METHODS

This retrospective study assessed psychiatric manifestations in pediatric SLE patients aged less than 18 years who received psychiatric consultation at Siriraj Hospital during the 2003 to 2012 study period. Siriraj Hospital is Thailand's largest university-based tertiary referral center and one of the national tertiary care centers for pediatric SLE. Medical records were reviewed for demographic and clinical characteristics, including presenting psychiatric symptoms, clinical symptoms, organ involvement of SLE, laboratory results, psychiatric diagnoses, and psychiatric treatments and outcomes. Patients with underlying psychiatric or neurodevelopmental disorders were excluded. The protocol for this study was approved by the Siriraj Institutional Review Board (SIRB-COA number SI 743/2013).

Demographic and clinical data were analyzed using descriptive statistics. Factors associated with the diagnosis of NPSLE were analyzed using Fisher's exact test. All statistical analyses were conducted using SPSS (PASW) Statistics version 18 (IBM, Armonk, NY).

RESULTS

During the ten-year study period, 158 new pediatric SLE cases received treatment at our center and 35 cases received a psychiatric consultation for evaluation and management of their psychiatric symptoms. Of the 35 cases, one case was excluded due to underlying Prader-Willi syndrome, oppositional defiant disorder, and moderate mental retardation. The remaining 34 cases were included. Background characteristics of patients are shown in Table 1. The median age of the patients was 13 years (range: 6-17) and more than 80% were female. About 90% of these children were cared for by their biological parents and 60% lived in nuclear families. More than 60% of patients developed psychiatric symptoms within 1 year after their SLE diagnosis. Twenty-two patients had more than one organ system involvement with renal, hematologic, and dermatologic systems being the three most common involved organ systems.

Psychiatric symptoms and psychiatric diagnoses

Presenting psychiatric symptoms and psychiatric diagnoses made after the psychiatric consultation are shown in Table 2. The three most common presenting psychiatric symptoms were mood disturbances (mostly depressed mood),

Table 1
Background characteristics.

Characteristics (*N*=34)	*n* (%)
Gender, female	28 (82.4)
Age: 12.4 ± 2.7 (mean ±SD)	
Caretaker	
Biological parents	31 (91.2)
Relatives	3 (8.8)
Family type	
Single	20 (58.8)
Extended	14 (41.2)
Number of siblings	
None	6 (17.6)
≥ 1	28 (82.4)
Duration of SLE prior to developing psychiatric symptoms	
< 1 year	22 (64.7)
≥ 1 year	12 (35.3)
Number of organ system involved by SLE	
≥ 2	22 (64.7)
1	12 (35.3)
Organ system involved by SLE	
Renal	28 (82.3)
Hematologic	15 (44.1)
Dermatologic	13 (38.2)
Nervous system	11 (32.4)
Pulmonary	7 (20.6)
Cardiovascular	5 (14.7)
Musculoskeletal	3 (8.8)
Gastrointestinal	1 (2.9)

anxiety and behavioral change. Some patients presented with more than one psychiatric symptom.

Sixteen patients (47.1%) were diagnosed as having psychiatric symptoms resulting from nervous system involvement of SLE (NPSLE). Among those, the diagnoses according to DSM-IV-TR were as follows: mood disorder due to SLE (9 cases), psychotic disorder due to SLE (4 cases), and delirium (3 cases). Thirteen patients were diagnosed as having psychiatric disorders not related to NPSLE. These diagnoses included adjustment disorder (6 cases), depressive disorder (3 cases), anxiety disorder (2 cases), somatoform disorder (1 case), and steroid induced mood

Table 2
Psychiatric symptoms and psychiatric diagnoses among pediatric SLE patients who received psychiatric consultation.

Psychiatric symptoms and diagnoses (*N* = 34)	*n* (%)
Presenting psychiatric symptoms	
Mood disturbances	21 (61.8)
Anxiety	8 (23.5)
Behavioral change	7 (20.6)
Cognitive dysfunction	6 (17.6)
Sleep disturbance	4 (11.8)
Psychotic symptoms	3 (8.8)
Pain	2 (5.9)
Psychiatric diagnoses	
Neuropsychiatric SLE	16 (47.1)
Mood disorder due to SLE (*n*=9)	
Psychotic disorder due to SLE (*n*=4)	
Delirium (*n*=3)	
Adjustment disorder	6 (17.6)
Depressive disorder	3 (8.8)
Anxiety disorder	2 (5.9)
Somatoform disorder	1 (2.9)
Steroid induced mood disorder	1 (2.9)
Normal psychological reaction	5 (14.7)

disorder – depressive type (1 case). The other five patients were diagnosed as having a normal psychological reaction to their illness (*ie*, no psychiatric disorders). Clinical manifestations in 16 patients with NPSLE are shown in Table 3.

Management of psychiatric symptoms

All patients received psychological management, including behavioral interventions, psychological support to the patient and family, and other supportive interventions. Patients with diagnoses of NPSLE, which included delirium, mood disorder due to SLE, and psychotic disorder due to SLE, were treated by adding or increasing the dosage of anti-inflammatory medications. Psychotropic medications were given to most patients with mood disorder due to SLE and psychotic disorder due to SLE, but they were not given to patients with delirium. Psychiatric symptoms improved in most patients after receiving treatment. Exceptions included three patients with psychotic disorder due to SLE, of which one was loss to follow-up and two died from septicemia.

Relationship between diagnosis of NPSLE and clinical characteristics

The Fisher's exact test was used to assess the relationship between a diagnosis of NPSLE and clinical characteristics. The clinical characteristics

Table 3
Clinical Manifestations of NPSLE.

Gender, age(years)	Psychiatric symptoms	Other organ involvement of SLE	Psychiatric diagnosis
F, 11	Aggressive behavior and disorientation	Lupus nephritis class IV Thrombotic microangiopathy CNS vasculitis	Delirium
F, 13	Confusion and depressed mood	Lupus nephritis class IV Pericarditis Thrombocytopenia	Delirium
F, 15	Confusion and hallucination	Lupus nephritis class IV with increasing hematuria	Delirium
F, 6	Aggressive behavior, depressed mood, lethargy, and poverty of thought	Lupus nephritis class IV CNS vasculitis	Mood disorder due to SLE
F, 11	Depressed mood	Lupus nephritis class IV Pericarditis Pleuritis	Mood disorder due to SLE
F, 12	Depressed mood and anxiety	Lupus nephritis class IV Recent onset of pericarditis Lymphopenia and thrombocytopenia	Mood disorder due to SLE
F, 13	Aggressive behavior, depressed mood, and sleep difficulty	Lupus nephritis class II CNS vasculitis Pericarditis	Mood disorder due to SLE
F, 13	Depressed mood	Lupus nephritis class IV Pleuritis CNS vasculitis	Mood disorder due to SLE
F, 14	Cognitive dysfunction and depressed mood	CNS vasculitis Gastritis due to vasculitis	Mood disorder due to SLE
F, 14	Depressed mood and sleep difficulty	Lupus nephritis class IV Cutaneous vasculitis	Mood disorder due to SLE
F, 14	Anxiety, depressed mood, lethargy, and catatonia	Lupus nephritis class IV CNS vasculitis Pancytopenia	Mood disorder due to SLE
F, 15	Depressed mood, behavioral change, and cognitive dysfunction	Lupus nephritis class IV CNS vasculitis	Mood disorder due to SLE (bipolar type)
F, 8	Cognitive dysfunction, hallucination, and sleep difficulty	Lupus nephritis class II CNS vasculitis	Psychotic disorder due to SLE
F, 8	Behavioral change, catatonia, and visual hallucination	Lupus nephritis class IV CNS vasculitis	Psychotic disorder due to SLE
F, 10	Aggressive behavior and delusion	Lupus nephritis class III CNS vasculitis Autoimmune hepatitis	Psychotic disorder due to SLE
F, 16	Sleep difficulty, delusion, and behavioral change	Lupus nephritis class II CNS vasculitis	Psychotic disorder due to SLE

Table 4
Factors associated with the diagnosis of NPSLE.

	NPSLE *n/N*	Non NPSLE *n/N*	*p*-value
Number of organ involvement ≥2	15/16	7/18	0.001
Presence of nervous system involvement	11/16	0/18	0.000
Presence of cognitive dysfunction	6/16	0/18	0.006

associated with the NPSLE diagnosis included presence of more than one organ system involvement (p=0.001), presence of nervous system involvement (p=0.000), and presence of cognitive dysfunction (p=0.006) as shown in Table 4. Patient age, presence of involvement in other organ systems, presence of other psychiatric symptoms, and timing between onset of psychiatric symptoms and diagnosis of SLE were not statistically different between NPSLE and non-NPSLE patients.

DISCUSSION

We retrospectively reviewed clinical manifestations in 34 pediatric SLE patients who had psychiatric symptoms and received psychiatric consultation at a tertiary care hospital in Thailand. It is common practice at our center that SLE patients with psychiatric symptoms receive a psychiatric consultation. Although there may have been some patients with psychiatric symptoms that did not receive psychiatric consultation for some reasons, we assumed that almost all SLE patients with psychiatric manifestations during the study period were included in this review.

The majority of our patients developed psychiatric symptoms within one year after SLE diagnosis consistent with a finding from two previous studies. (Benseler and Silverman, 2007; Lim *et al*, 2013). We found that common psychiatric presentations were mood disturbances, anxiety, behavioral change, and cognitive dysfunction. Common psychiatric diagnoses included mood disorder due to SLE, adjustment disorder, psychotic disorder due to SLE, and delirium.

The psychiatric symptoms found in our study were consistent with those reported from previous studies in pediatric NPSLE, including cognitive dysfunction, mood disorder, and psychosis (Olfat *et al*, 2004; Yu *et al*, 2006; Benseler and Silverman, 2007; Singh *et al*, 2009; Muscal *et al*, 2010; Lim *et al*, 2013). Psychiatric symptoms reported in previous studies were symptoms caused by neurological involvement of SLE or NPSLE only. None of these studies described other psychiatric symptoms not associated with NPSLE. The present study describes psychiatric manifestations in SLE patients resulting from both NPSLE and conditions not related to NPSLE. Psychiatric symptoms from conditions not related to NPSLE were found in about half of our patients. This finding highlights the fact that, not only brain involvement of SLE, but also psychological factors play a major role in causing psychiatric morbidity in this patient population.

Diagnosis of NPSLE or mental disorders due to a medical condition by DSM-IV-TR diagnostic criteria requires clinical information suggesting that the psychiatric symptoms result from a direct pathophysiological effect of a medical illness (American Psychiatric Association, 2000). In the case of SLE, this diagnosis would be based on the correlation of psychiatric symptoms and evidence of active neurological involvement, such as abnormal neurological signs, seizure, abnormal neuroimaging, presence of NPSLE-associated autoantibodies, inflammatory markers of NPSLE, or other evidence of the disease being active

(Borchers *et al*, 2005; Stojanovich *et al*, 2007). In this study, diagnosis of NSPLE was made by experts on the psychiatric consultation team and was based on the immediately aforementioned standard guidelines. Such diagnosis is sometimes difficult to make, as it is based mainly on clinical information without any specific diagnostic psychological testing. As such, the identification of factors that correlate with this diagnosis may be helpful in more accurately and more quickly diagnosing this disorder in clinical practice. In this study, the factors that statistically significantly correlated with diagnosis of NPSLE included organ system involvement ≥ 2, presence of nervous system involvement, and presence of cognitive dysfunction. These clinical characteristics, particularly the presence of cognitive dysfunction, may be helpful in alerting clinicians to the possibility of NPSLE when evaluating SLE patients with psychiatric symptoms. Cognitive dysfunction was found to be one of the most common symptoms in pediatric NPSLE patients with psychiatric manifestations. In one study of 53 pediatric SLE patients with psychiatric illness, cognitive dysfunction was found in all patients, with some patients also presenting with psychosis and/or depressive symptoms (Lim *et al*, 2013).

All patients with NPSLE in this study received anti-inflammatory medications and patients with psychosis and depression also received psychotropic medications. Most of these patients recovered from their psychiatric symptoms, except for two patients with NPSLE who died from other complications of SLE. This finding supports a previous study that reported that NPSLE is associated with increased mortality (Benseler and Silverman, 2007).

This study has some mentionable limitations. First, this study was conducted in a university-based national tertiary referral hospital and most patients were referred complicated cases. As such, the data from this study may not accurately represent patients and conditions in other settings. Second, it was possible that some patients with mild psychiatric symptoms did not receive psychiatric consultation and were not included in our review. These potentially missing patients may have had milder psychiatric symptoms not recognized by their attending physicians or they may have had critical medical conditions that rendered psychiatric consultation unnecessary or unachievable. Third, the sample size was small because SLE was not a common illness in pediatric population and only patients with psychiatric symptoms who received psychiatric consultation were recruited. Consequently, it was not possible to use a multivariate analysis to demonstrate the association between the three clinical characteristics and the diagnosis of NPSLE, and the Fisher's exact test was used instead. Finally, and consistent with all retrospective studies, medical record data may have been inaccurate or missing in some cases. Despite these limitations and given the lack of data on psychiatric manifestations in pediatric SLE, the results from this study provides information on clinical characteristics of pediatric SLE patients with psychiatric presentations and provides suggested clinical clues that can alert clinicians to a diagnosis of NPSLE.

In conclusion, psychiatric manifestations among pediatric SLE patients included a variety of presentations. The diagnosis of NPSLE was found to be significantly associated with the presence of multiple organ involvement, presence of nervous system involvement, and presence of cognitive dysfunction. This study highlights the importance of careful assessment and appropriate treatment of psychiatric manifestations, particularly NPSLE. NPSLE appears to have a less favorable prognosis and for which treatment with anti-inflammatory medications is required.

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