



PREVALENCE OF NEUROPSYCHIATRIC DISORDERS IN PATIENTS SUFFERING FROM SYSTEMIC LUPUS ERYTHEMATOSUS (SLE)

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ABSTRACT

Background: Neuropsychiatric systemic lupus erythematosus (NPSLE) is a serious and well-known complication of systemic lupus erythematosus (SLE). There is limited evidence about the prevalence of NPSLE and its manifestations. The aim of this study was to estimate the prevalence of NPSLE in different populations. **Methods:** We searched PubMed from 2009 to June 2019 to identify studies relevant to this review. Database searches combined terms from three themes: (1); (2); (3) mortality terms were searched as both keywords (title/abstract words) and subject headings, as appropriate. We also examined the records from the papers and NPSLE was characterized using the American College of Rheumatology case definitions. **Result:** We identified 105 articles which are relevant, 79 of which were excluded on the basis of abstract analysis. The remaining 26 articles were reviewed in its full text and 9 were included in the final analysis. The major neuropsychiatric comorbidities that we observed from the studies were Major depression, headaches, seizures and cerebrovascular diseases. 17%-52.3% of people had Major depression out of overall NPSLE patients, prevalence of headaches were from 38.8% to 60% of NPSLE. The NPSLE patients who suffered from seizures were from 26.4% to 63%; Finally, the data of cerebrovascular diseases whose prevalence in NPSLE patients ranged from 26% to 38.8%. The overall prevalence of Neuropsychiatric SLE is 11.3%-60% of all SLE patients. **Conclusion:** SLE have a very prevalence of having the neuropsychiatric manifestations including major depression, seizures, cerebrovascular disease and other manifestations also are seen including the physical and social suffering. Continued studies into the pathogenesis of neurological involvement in patients with SLE are warranted. **Categories:** Neurology, Psychiatry, Allergy/Immunology.

KEYWORDS: Neuropsychiatric sle, cvd & sle, sle induced psychosis, co-morbid of sle, systemic lupus erythematosus (sle).

INTRODUCTION AND BACKGROUND INTRODUCTION

Systemic Lupus Erythematosus disease is a chronic autoimmune disease with unknown etiology that affects multiple organ systems including joints, skin, heart, lungs, kidneys and nervous system. The prevalence of this disease in the US is 52.2/100,000.

The most prevalent are the arthritis with arthralgia and cutaneous lupus erythematosus. Both high prevalence and visible manifestations explain an important role that has always been ascribed to the skin lesion in the SLE diagnosis. SLE is found to be more common in women by having a nine times higher incidence rate than men.

Neuropsychiatric systemic Lupus Erythematosus (NPSLE) is a clinical feature which is characterized by the neurological syndromes of the central nervous

system, peripheral nervous system. The involvement of the CNS and PNS is a severe complication and is a significant cause of morbidity and mortality and can have adverse effects on patients quality of life. CNS-NPSLE is the third leading cause of SLE related death after kidney involvement and secondary infections.

NPSLE shows some similarities with the neuro Behcet's disease (NBD) as both conditions have some analogous clinical features and they are pathologically associated with cerebral vasculopathy. Behcet's disease (BD) is a multisystem inflammatory disorder dominated clinically by recurrent oral and genital ulceration, uveitis, and erythema nodosum. The disease tends to wax and wane. BD is a vasculitis, affecting vessels of different types, sizes, and localizations. Although the cause of BD is unknown, autoimmune, infectious, and genetic causes have been suspected. Environmental factors, such as

microbial infections, are also suspected to be factors that contribute to the development of BD. Central nervous system (CNS) involvement can be either parenchymal or nonparenchymal. Parenchymal involvement primarily affects the brain stem, spinal cord, and cerebral hemispheres. Non Parenchymal involvement includes intracranial hypertension, aseptic meningitis, cranial neuropathy, and cerebrovascular disorders such as dural sinus thrombosis, arterial dissection, occlusion, and aneurysm. The prevalence of psychological symptoms was remarkable in patients with BD. The psychological symptoms in BD could be aggravated by the illness itself or by the immunosuppressive drugs used during the treatment course. Psychiatric reactions to BD may include anxiety, insomnia, manic/depressive episodes and psychosis. The characteristic MRI brain lesions in parenchymal involvement of BD is an upper brainstem lesion that extends into the thalamus and basal ganglia on one side.

The CNS-NPSLE pathogenesis is not yet known but there are some specific findings that can be seen at the time of diagnosis of CNS-NPSLE and they are more considered by the researchers to be the cause of it. CNS-NPSLE, and autoantibodies and cytokines are believed to play a part. We determined the IL-10, IL-6, IL-8 and IFN- γ levels in the serum and cerebrospinal fluid (CSF) of CNS-NPSLE patients, non-CNS SLE patients, patients with intracranial infection and normal subjects. The differences in cytokine levels were compared. Logistic regression analysis was performed to analyze the correlations between the levels of these cytokines and MRI findings in CNS-NPSLE. Other pathogenesis that to be considered for CNS-NPSLE can be hemorrhage, ischemia and other microvasculature related complications

There are multiple symptoms that are seen when the CNS and PNS is involved so it is not easy to sort the cause of the symptom to the CNS-NPSLE but In 1999, the American College of Rheumatology (ACR) developed case definitions for 19 NPSLE syndromes to standardize definitions, diagnostic criteria, and diagnostic testing of this disorder. NPSLE manifestations consists of 19 NPSLE syndromes, namely aseptic meningitis, cerebrovascular disease (CVD), demyelinating syndrome (e.g., multiple sclerosis) headache, movement disorder, myelopathy, seizure disorder, acute confusional state, anxiety disorder, cognitive dysfunction, mood disorder, psychosis, Guillain-Barre syndrome, autonomic neuropathy, mononeuropathy (single/multiplex), myasthenia gravis, cranial neuropathy, plexopathy, and polyneuropathy.

REVIEW

METHODS

This is a systematic review. We search for relevant studies in English for the following databases from the emergence condition to December 2019: PubMed (2009-2019). Studies we included from the past 10 years.

The keywords used "systemic lupus erythematosus", "SLE", "Lupus disorder", "butterfly rash", "central nervous system manifestations", "CNS involvement", "neurological symptoms", "Neuropsychiatric impairment", "Mental disorders", "delusions", "headache", "seizures", "psychosis", "depression", "anxiety", "cognitive impairment", "cerebrovascular disease"

Inclusion and Exclusion Criteria. Articles not published in English, letters, summaries, dissertations, theses, and case reports were excluded as well as studies that used children or animal models and studies that were not related to central nervous system complications of SLE. Studies were included only if diagnosis of neurological complications was made by expert neurologists. Only studies with neurological complications primary or secondary to SLE. MRI, ECLAM and SLEDAI-SELENA Modification scores were used to evaluate disease activity and SLICC/ACR Damage Index was used to assess accumulated damage, ACR criteria, Mini-Mental State Examination (MMSE) and Clock Drawing Test (CDT) were included.

RESULTS

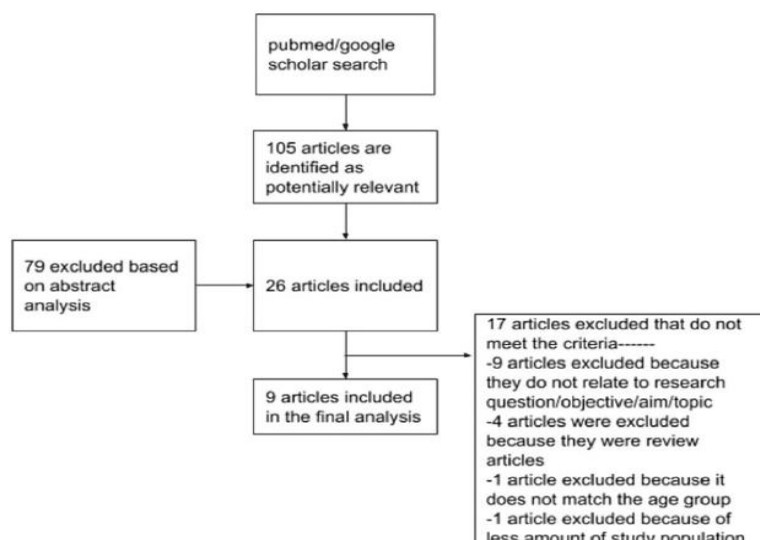


FIGURE 1: Research process flowchart.

Figure 1 described search identified 105 articles which are relevant, 79 of which were excluded on the basis of abstract analysis. The remaining 26 articles were reviewed in its full text and 9 were included in the final analysis. Most of the studies were cross-sectional studies: one was a retrospective study and two were cohort studies. Figure 1 summarizes the major findings of each study including the diagnostic criteria that was used

to diagnose the SLE patients with neuropsychiatric symptoms and also describes the study design.

Based upon evidence of the studies and using critical appraisal we were able to perform qualitative data synthesis and organize the data and summarize the findings.

Table 1: Demographics of the studies included.

Author/ Article	Country	Total no. of people	No. of patients with SLE(n)	Controls	Male (n)cases	Female(n) cases	Mean disease duration	Mean age	Known cases of CNS involvement	New cases of CNS involvement
Etemadifar et al.,2016 [1]	iran	121	121	0	27	94	NR	NR	NR	NR
Kampylafka et al.,2013 [2]	Greece	370	370	0	43	327	5.7±8.2	32±/-14	0	370
Tomaz howro et al., 2011 [3]	poland	52	52	0	3	46	NR	42.46 ± 12.75 years	NR	NR
Benchalak maneeton et al., 2010 [4]	thailand	52	30	22	0	52	5.5 ± 4.3 with CNS involvement 8.1 ± 5.9 with no CNS involvement	36.1 ± 12.0 with CNS involvement and 31.3 ± 8.2 with no CNS involvement	11	19
Abdelraheem et al.,[5]	egypt	128(including patients with behcet disease)	50	44	6(p=0.8)	44(P=0.8)	7.5±2.3 (P=0.1)	29.5±11.5 (p=0.3)	NR	NR
Wiseman SJ et al.,	United Kingdom	102	51	51	4	47	2 to 12.3 years	48.8 ± 14.3 years)	NR	NR
Borhani Haghighi.,	Iran	407	407	0	4	42	4 years	24	46	361
John hanly et al.,	NR	1,827	1827	0	203	1624	5.6±4.8 months and follow-up 4.73±3.45 years	35.1±13.3	1,627	200
Mahdavi Adeli A et al.,	iran	102	54	48	13	89	98.66 ± 99.95 months	34.38 ± 11.37	NR	NR

Table 1 summarizes the demographics of the studies which include article/author, country where the study has taken place, total no. of people recruited for the study, no. of cases(patients suffering from SLE), controls

(recruits who don't have SLE), the number of male patients, number of female patients, mean disease duration, mean age, known and unknown cases of CNS involvement.

TABLE 2: Prevalence of the major neuropsychiatric manifestations in NPSLE patients.

Article/Author	Major depression	Anxiety	Seizures	CVD	Headaches	Cognitive deficits
Etemadifar et al.,2016 [1]	NR	8%	26.4%	38.8%	38.8%	11.6%
Kampylafka et al.,2013 [2]	NR	NR	35%	26%	NR	NR
Tomaz howro et al., 2011 [3]	NR	NR	NR	NR	NR	NR
Benchalak maneeton et al., 2010 [4]	NR	NR	NR	NR	NR	45.5%
Abdelraheem et al.,[5]	38%	22%	NR	NR	NR	42%
Wiseman SJ et al.,2016[6]	NR	NR	NR	NR	NR	NR
Borhani Haghighi et al., 2010[7]	17%	NR	63%	28.3%	60%	NR
John G hanly et al., 2015[8]	52.3%	NR	NR	NR	NR	NR
Aliyeh Mahdavi Adeli et al., 2016[9]	NR	NR	NR	NR	NR	33.33%(p=0.006)

Table 2 summarizes the major neuropsychiatric symptoms and their data based on all the nine articles. Articles Borhani Haghighi et al., 2010^[7] and John G hanly et al., 2015^[8] describe the overall prevalence of NPSLE as 11.3%-60% of SLE patients.

The major neuropsychiatric comorbidities that we observed from the studies were Major depression, headaches, seizures and cerebrovascular diseases. Tomaz howro et al., 2011^[3], Abdelraheem et al.,^[5], Borhani Haghighi et al., 2010^[7] and John G hanly et al., 2015^[8] are the articles that included the data of Major depression and its relation to SLE. In Tomaz howro et al., 2011^[3] study 11.54% of people had Major depression out of overall SLE, In Abdelraheem et al.,^[5] 38% of NPSLE patients suffered, in Borhani Haghighi et al., 2010^[7] it was about 17% of the NPSLE patients and in John G hanly et al., 2015^[8] it was about 52.3% of the NPSLE patients. The data for headaches were summarized from Etemadifar et al., 2016^[1] and Borhani Haghighi et al., 2010^[7] which had patients suffering from headaches ranging from 38.8% to 60%of NPSLE. The NPSLE patients who suffered from seizures were from 26.4% to 63% ; the data was provided in articles Etemadifar et al.,2016^[1], Kampylafka et al., 2013^[2] and Borhani Haghighi et al., 2010.^[7] Finally, the data of cerebrovascular diseases whose prevalence in NPSLE patients were ranging from 26% to 38.8% were extracted from studies Etemadifar et al.,2016^[1], Tomaz howro et al., 2011^[3] and Borhani Haghighi et al., 2010.^[7]

In Etemadifar et al., 2016^[1] 121 (21.7%) patients who were diagnosed as NPSLE (neuropsychiatric systemic lupus erythematosus) are enrolled in the study. Of whom, 94 patients were female (77.7%) and 27 patients were male (22.3%) with a female to male ratio of 3.48:1. The most common NPSLE manifestations were headache (38.8%), cerebrovascular disease (CVD) (38.8%) and seizure (26.4%). Thirty-nine patients have psychiatric disorders. Among them, 32 patients (26.4%) have

periods of psychosis and mood disorder was found in 6 patients (5%). During the study six patients passed away due to neurological involvement. Most of them were female and had an early onset of the disease i.e. before the age of 25.

In Kampylafka et al., 2013^[2] 370 patients suffering from SLE were recruited out of which 16/370 (4.3%) patients presented with a total of 23 major CNS events. These included seizures (35%), strokes (26%), myelopathy (22%), optic neuritis (8.7%), aseptic meningitis (4.3%) and acute psychosis (4.3%). Incidence was 7.8/100 person years. Among hospitalizations for SLE, 13% were due to CNS manifestations. Epileptic seizures were associated with high disease activity, while myelopathy correlated with lower disease activity and NMO-IgG antibodies (P40.05). Stroke incidence correlated with APS coexistence (P=0.06). Overall, CNS involvement correlated with high ECLAM and SLEDAI scores (P<0.001).

In Tomaz howro et al., 2011^[3] Mental disorders were diagnosed in 16 (30.77%), depressive disorder in 6 (11.54%), cognitive dysfunction in 5 (9.62%), anxiety disorder in 4 (7.69%) and psychosis in one patient (1.92%). SLE duration was shorter in patients diagnosed with an anxiety disorder (P < 0.05), and cumulative dose of corticosteroids was lower in patients with anxiety disorder (P < 0.01). There was high positive correlation between SLE duration and cumulative dose of corticosteroids (r = 0.684, P < 0.001).

In Benchalak maneeton et al., 2010^[4] study only information regarding the cognitive deficits was studied. Cognitive impairment was identified in 9 (30.0%) SLE patients [5 (45.5%) with previous history of CNS involvement and in 4 (21.1%) SLE with no previous history of CNS involvement compared to 0% in the control group.

In Borhani Haghighi et al., 2010^[7] study 407 patients were recruited out of which 11.3% had neuropsychiatric complications. The most frequent findings were seizure (63%), headache (60%), and decreased level of consciousness (50%). Cerebrovascular disease (28.3%), seizure disorder (26.5%), and acute confusional state (19.6%).

In John G hanly et al., 2015^[8] study 1,827 patients with SLE were recruited, 88.9% were female, and 48.9% were Caucasian. The mean $\pm$ SD age of the patients was 35.1 ± 13.3 years, disease duration was 5.6 ± 4.8 months, and the length of follow up was 4.7 ± 3.5 years. During the course of the study, 863 (47.2%) of the 1,827 patients had 1,627 neuropsychiatric events. Mood disorders occurred in 232 (12.7%) of 1,827 patients, and 98 (38.3%) of 256 mood disorder events were attributed to SLE. The estimated cumulative incidence of any mood disorder after 10 years was 17.7% (95% confidence interval 15.1, 20.2%)

In Aliyeh Mandavi Adeli et al., 2016^[9] study 54 patients with SLE and 48 healthy subjects were included. The mean MMSE(mini mental status examination) scores in SLE and control group patients (26.12 ± 3.58 and 28.01 ± 1.99 , respectively) were significantly different ($P = 0.001$). The sub-scores in all areas assessed with MMSE were lower in SLE patients; however, it was only significant in the areas of orientation, recall and language ($P < 0.05$). SLE patients showed a significantly poorer performance in TMT (trail making test) compared to healthy controls ($P = 0.01$).

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Based upon evidence of the studies and using critical appraisal we were able to perform qualitative data synthesis and organized the data and summarize the findings. Table 1 summarizes the demographics of the studies which include article/author, country where the study has taken place, total no. of people recruited for the study, no. of cases(patients suffering from SLE), controls(recruits who don't have SLE), the number of male patients, number of female patients, mean disease duration, mean age, known and unknown cases of CNS involvement.

DISCUSSION

Based on the results we found, the patients suffering from Systemic lupus erythematosus are at high risk of developing neuropsychiatric diseases (11.3%-60%). Based on a wide range of article patients with SLE are at high risk of developing neuropsychiatric comorbidities

such as headaches, seizures, major depressive disorders and cerebrovascular diseases.

Overall prevalence seems to vary widely among the studies which can be due to many factors such as selection bias, the difference in the mean age of the duration of the disease, racial differences, differences in the diagnostic factors and several other factors.

This study is consistent with the previous studies. The results we produced were very similar to the other review articles on this topic. Previous review articles were able to point out similar findings for the Major depression, headaches and seizures. In this article we were able to show the relation of these disorders and SLE. Additionally we also found out that Cerebrovascular diseases are also common in patients with SLE.

One key strength of this article is the articles included in this review are conducted within ten years and are taken from renowned journals. the mean age of duration of the disease is similar in most of the articles. we also included the diagnostic criteria which were used by individual articles in Figure 1. The common findings were also identified and mentioned. the demographics which include age, sex, mean disease duration, cases, controls, known cases of CNS and new cases were also collected and are mentioned in table I. Two articles Kampylafka et al., 2013^[2] and Benchalak maneeton et al., 2010^[4] also provided the details about new and old cases with CNS involvement. The major neuropsychiatric symptoms and their prevalence in the studies conducted were summarized in Table 2.

In this systematic review the common neuropsychiatric comorbidities were headaches(present in 38.8% to 60% of NPSLE), seizures(26.4% to 63% of NPSLE) and major depressive disorder(17% to 52.3% of NPSLE), although the prevalence of mild depression were much higher. The prevalence of cerebrovascular diseases such as strokes were high ranging from 26% to 38.8% of NPSLE patients which would be important considering those are one of the neuropsychiatric comorbidities which can be life threatening.

Not withstanding, this review is not without its limitations. There were a small number of studies available for analysis. The diagnostic criteria used by the studies were different, which can be attributed to the variability in the results. MRI findings were used in articles Etemadifar et al.,2016^[1] and Abdelraheem et al.,^[5] and the Mini mental status examination (MMSE) was used by Tomaz howro et al., 2011^[3], Benchalak maneeton et al., 2010^[4] and Aliyeh Mandavi Adeli et al., 2016.^[9] The details of the diagnostic criteria are mentioned in the Table 2. Most of the patients that were included in the study were on medications such as immunosuppressive drugs (eg. Methotrexate) and corticosteroids and the information on the extent of their adverse effects were not studied. The effects of

corticosteroids had positive correlation to anxiety disorder which was described in Tomaz howro et al., 2011^[3] study. Further research has to be done to assess the adverse effects.

This systematic review points out that the patients who are suffering from systemic lupus erythematosus have increased risk of developing neuropsychiatric comorbidities such as Major depression, headaches, seizures and cerebrovascular diseases. Due to which both physicians and psychiatrists have to assess the patient for these symptoms and treat accordingly.

CONCLUSIONS

Despite the limitations, the systematic review points out that patients with SLE have very high risk of having neuropsychiatric manifestations such as Major depression, headaches, seizures and cerebrovascular disease. The high frequency of Cerebrovascular diseases in NPSLE need special attention because they can be life threatening.

More detailed studies to assess the neurological, psychological, genetic and autoimmune role of SLE are needed. Despite the technical and scientific advances, the SLE remains a threatening and chronic condition, causing intense physical, psychological and social suffering. More studies with larger numbers of subjects with and without SLE using scales and standardized diagnostic criteria are needed.

Both doctors and psychiatrists should be suspicious about any neurological and psychological symptoms in patients suffering from SLE as they are very common.

Additional Information

DISCLOSURES

Conflicts of interest: In compliance with the ICMJE uniform disclosure form, all authors declare the following: **Payment/services info:** All authors have declared that no financial support was received from any organization for the submitted work. **Financial relationships:** All authors have declared that they have no financial relationships at present or within the previous three years with any organizations that might have an interest in the submitted work. **Other relationships:** All authors have declared that there are no other relationships or activities that could appear to have influenced the submitted work.

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