

# Is it relevant to screen young women hospitalized in psychiatric department for neuropsychiatric systemic lupus erythematosus (NPSLE)?

## A prospective study of 100 psychiatric inpatients

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### Abstract

On the basis that diagnosis of neuropsychiatric systemic lupus erythematosus (NPSLE) is sometimes difficult and systemic lupus erythematosus (SLE) can present with isolated psychiatric symptoms, we initiated a survey in a psychiatric department to screen for NPSLE in young female inpatients.

We prospectively studied consecutive young female patients referred to the department of psychiatry. Antinuclear antibodies (ANA), anti-deoxyribonucleic acid (DNA), and antiextractable soluble nuclear antigens (ENA) in the serum of patients were screened. In case of positive anti-DNA or anti-ENA, the patient was referred to the department of internal medicine.

One hundred patients were enrolled, mean age  $33.1 \pm 8.4$  years. Most patients presented underlying psychiatric disorders: depression (46%), schizophrenia (13%), anxiety disorder (6%), and personality disorder (10%). A quarter of the cohort did not display underlying psychiatric disorders before hospitalization. Positive ANA  $\geq 1:160$  were found in 32 of the 100 patients tested (32%). No patients presented anti-DNA antibodies. One patient had positive anti-sjögren's syndrome related antigen A (SSA), but did not present any features of SLE or Sjögren syndrome.

Thus, systematic screening of SLE is not relevant in young women hospitalized in psychiatric department. However, clinicians should keep in mind that SLE can present with pure psychiatric symptoms.

**Abbreviations:** ANA = antinuclear antibodies, DNA = deoxyribonucleic acid, ENA = antiextractable soluble nuclear antigens, NPSLE = neuropsychiatric systemic lupus erythematosus, SSA = sjögren's syndrome related antigen A, SLE = systemic lupus erythematosus.

**Keywords:** mental illness, neuropsychiatric systemic lupus erythematosus, psychiatric disorder, systemic lupus erythematosus

## 1. Introduction

Systemic lupus erythematosus (SLE) is an autoimmune disease which particularly affects young women, with a prevalence of 50 to 150/100,000 in Caucasians.<sup>[1,2]</sup> Neuropsychiatric SLE (NPSLE) was first described by Hebra and Kaposi in 1875 in patients presenting with stupor.<sup>[3]</sup> NPSLE is frequent, from 18% to 69%, depending on the study and the definition of NPSLE.<sup>[4,5]</sup>

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Long-term patient survival of individuals with NPSLE has strongly improved over the past decades, but involvement of the central nervous system (CNS) is one of the major causes of morbidity and mortality in patients with SLE.<sup>[6]</sup>

NPSLE is often difficult to diagnose, as there is no simple diagnostic test available. Brain biopsy is the only known definitive test able to diagnose NPSLE, however it is rarely performed. Autopsy data revealed that NPSLE is characterized by involvement of small vessel, microinfarcts, and hemorrhage.<sup>[7]</sup> Authentic vasculitis is rare. Magnetic resonance imaging (MRI) and examination of the cerebrospinal fluid are often necessary but normal investigations do not rule out the diagnosis of NPSLE.<sup>[8]</sup> There is no immunological signature of NPSLE, presence of antiribosomal P antibodies is not specific of NPSLE.<sup>[9]</sup>

NPSLE encompasses a wide spectrum of neurologic features ranging from strokes, seizures, peripheral neuropathy, chorea, dementia, but patients can present with pure psychiatric symptoms such as anxiety disorder, psychosis, and depression. Around 20 different clinical manifestations of neuropsychiatric syndromes associated with SLE were described by the American College of Rheumatology.<sup>[10]</sup> Treatment of NPSLE continues to present a major therapeutic challenge for the clinician in daily practice. Clinical trials have shown that cyclophosphamide (CYC) with corticosteroids are effective in achieving remission in NPSLE.<sup>[11]</sup> Plasma exchanges have also been described to be effective in refractory CYC NPSLE through small size case

series.<sup>[12,13]</sup> Recently, rituximab effectiveness in refractory NPSLE has also been described in several case reports and noncontrolled trials.<sup>[14]</sup>

On the basis that diagnosis of NPSLE is difficult and NPSLE can present with pure psychiatric symptoms, we therefore initiated a survey in a psychiatric department in France to screen NPSLE in young female inpatients. Indeed, earlier detection and treatment of NPSLE could strongly decrease damages.

## 2. Methods

### 2.1. Patients

We prospectively studied consecutive patients referred to the department of psychiatry in a French University hospital (Centre Hospitalier de Caen) from June 2011 to January 2015. All newly referred female inpatients between 18 and 55 years were proposed to be recruited for the survey. Exclusion criterion was already known SLE. All patients provided written informed consent and this survey was conducted in compliance with the protocol of Good Clinical Practices and Declaration of Helsinki principles. This study was also carried out with the approval of the Regional Ethics Committee Caen (Northwest 3).

### 2.2. Immunological assay

Antinuclear antibodies (ANA), anti-deoxyribonucleic acid (DNA), and antiextractable soluble nuclear antigens (ENA) which include anti-sjögren's syndrome related antigen A (SSA) (52 and 60 kDa), anti-SSB, anti-Sm, anti-RNP, anti-Jo1, and anti Scl70, in the serum of patients were screened. ANA were detected using indirect immunofluorescence on HEp-2 cells. Isolation of double-stranded DNA and ENA were performed with enzyme-linked immunosorbent assay (ELISA). In the event of positive anti-DNA or anti-ENA, the patient was referred to the department of internal medicine to investigate the presence of SLE.

### 2.3. Clinical and biologic data

Clinical data were recorded for each patient at the time of hospitalization by the practitioners in charge of the patients with the use of a standardized form.

### 2.4. Statistical analysis

Descriptive statistics included the mean (standard deviation—SD) as appropriate for continuous variables, and frequency (percentage) for categorical variables. Statistical analyses

**Table 1**

#### Psychiatric patients' characteristics at baseline.

Epidemiological characteristics	
Female, n (%)	100 (100)
Age, y, mean, SD [min–max]	33.1 ± 8.44 [18–55]
Psychiatric disorder	
Depression, n (%)	46 (46)
Schizophrenia, n (%)	13 (13)
Anxiety disorder, n (%)	6 (6)
Personality disorder, n (%)	10 (10)
None	25 (25)

SD = standard deviation.

**Table 2**

#### Patients hospitalization characteristics at the time of inclusion in the survey.

Hospitalization	% (n)
Acute care unit	30 (30)
Conventional care unit	70 (70)
Cause of hospitalization	
Depression/suicide attempt	74 (74)
Anxiety	10 (10)
Psychosis/hallucination	12 (12)
Anorexia/bulimia	4 (4)

were performed using EpiData (EpiData Software version 2.0, “The EpiData Association” Odense, Denmark).

## 3. Results

### 3.1. Psychiatric patients' characteristics

One hundred one patients were enrolled in this survey. One patient was excluded because she was diagnosed as SLE few years ago and 1 patient declined it. The clinical characteristics of the 100 patients are shown in Table 1. All patients were female. The mean age at diagnosis was 33.1 ± 8.4 [18–55] years. Most patients presented underlying psychiatric disorders known before hospitalization: depression (46%), schizophrenia (13%), anxiety disorder (6%), and personality disorder (10%). A quarter of the cohort did not display chronic psychiatric disorders before hospitalization.

Table 2 shows the cause of each patients' hospitalization at time of inclusion in the survey. Among all patients, 74% were hospitalized for severe depression or a suicide attempt, 10% presented with a major anxiety episode, 12% presented with acute psychosis episodes, and 4% with anorexia. Seventy percent were hospitalized in a conventional care unit and 30% in acute care unit where the hospital stays were shorter.

### 3.2. Patient immunological characteristics

The results of the serological investigations are shown in Table 3. Positive ANA ≥1:160 were found in 32 of the 100 patients tested (32%). Two, 9, and 21 patients had, respectively, an ANA titer of 1:1280, 1:320, and 1:160. The fluorescence aspect was homogeneous in 1%, speckled in 90%, and nucleolar in 2%.

**Table 3**

#### Results of the serological investigations.

Patient immunological characteristics	% (n)
Antinuclear antibodies titer	
1:160	21 (21)
1:320	9 (9)
1:1280	2 (2)
Antinuclear antibodies fluorescence	
Homogeneous fluorescence	1 (1)
Speckled fluorescence	90 (90)
Nucleolar fluorescence	2 (2)
No fluorescence	7 (7)
Antidouble-stranded DNA	0 (0)
Anti-SSA	1 (1)

DNA = deoxyribonucleic acid, SSA = sjögren's syndrome related antigen A.

Seven patients did not display any fluorescence. Anti double-stranded DNA was not identified in any of the patients. One patient was positive for antibodies against ENA, anti-SSA.

### 3.3. Clinical assessment in internal medicine

The patient who displayed anti-SSA antibodies was referred to the department of internal medicine for SLE screening. After a clinical examination, she presented no features of SLE or Sjögren syndrome.

## 4. Discussion

During the 1970s, autoimmune mechanisms were proposed to explain the development of mental illness. Thus, many studies have focused on serological exploration of psychiatric patients, especially through antinuclear antibody screening. An association between psychiatric illness and ANA has been shown in various surveys. Depending on the study and definition of positive ANA, 7% to 30% of psychiatric patients have been shown present positive ANA.<sup>[15-17]</sup> The high prevalence of positive ANA first supports the hypothesis of an autoimmune mechanism of psychiatric disorder. More recently, associations between ANA and mental illness have been linked to drug treatment, particularly to lithium carbonate or chlorpromazine.<sup>[18,19]</sup> Drug-induced ANA is nowadays well known and excess of ANA rate in psychiatric patients can be clearly explained by drugs. Nevertheless, previous studies have not focused on more specific antibodies like anti-DNA antibodies or anti-ENA antibodies. The previous studies only explored biological aspects and the patients were not subsequently referred to rheumatology or internal medicine departments for clinical expertise.

On the basis that NPSLE can present with pure psychiatric symptoms, thus causing SLE diagnosis to be difficult, we conducted a prospective study enrolling 100 women. At first sight have included 100 patients could not seem to be enough because prevalence of SLE is rare but prevalence of SLE in young women is higher and prevalence of SLE in patients hospitalized for psychiatric symptom is not known but might be higher than in general population. However, our objective was not to answer to this question “Do undiagnosed NPSLE exist in a psychiatry department” but rather to answer to this one “Is it relevant to screen young women hospitalized in psychiatric department for neuropsychiatric systemic lupus erythematosus (NPSLE)?” We wanted to evaluate the “profitability” to systematically screen SLE in each young woman hospitalized in psychiatry, in other words our objective was to test a routinely screening of SLE in young women with mental illness. The rate of positive ANA was high, 32% of ANA  $\geq 1:160$ , according to the previous studies.<sup>[15-17]</sup> The prevalence of ANA in a healthy female population (2500 females between the ages of 20 and 50 years) showed that ANA  $>1:160$  could be found in less than 1% of individuals.<sup>[20]</sup> The high rate of ANA  $>1:160$  (32%) in our cohort was probably linked to the use of psychiatric drugs.

None of the patients included in this study had antidouble-stranded DNA antibodies. One patient had anti-SSA but did not present any features of SLE or Sjögren syndrome. Asymptomatic anti-SSA in female blood donors has previously been described as reaching 0.44% in a cohort of 5000 female blood donors.<sup>[20]</sup> Our study do not permit to diagnose SLE in this population of young female psychiatric inpatients, likely due to low prevalence of SLE

in the general population and does not support systematic screening of ANA in such populations in order to diagnose NPSLE.

Main limitation of the study is that only patients with anti-DNA or anti-ENA have been referred to the internal department. It is clear that, especially at the beginning of SLE, patients can present with ANA without anti-DNA or anti-ENA.<sup>[21]</sup> Thus it will be interesting to follow-up these patients to see if they later develop anti-DNA or anti-ENA.

On the other hand, as the prevalence of ANA in young females population is high (32% in this cohort), it would have been not relevant to choose a nonspecific antibody for a screening approach.

Thus, this study does not support systematic screening of SLE in young inpatients women hospitalized in psychiatric department. However, clinicians should keep in mind that SLE can present with pure psychiatric symptoms and mimic mental illness, especially during atypical presentation or refractory mental illness.

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