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PAPER

The development of a simple questionnaire to screen patients with SLE for the presence of neuropsychiatric symptoms in routine clinical practice

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Aim: The creation of a physician-administered questionnaire to screen patients with Systemic Lupus Erythematosus (SLE) for the presence of symptoms suggestive of neuropsychiatric involvement (NPSLE).

Methods: The development of the questionnaire followed three phases. First, a list of manifestations was prepared based on the ACR case definitions for NPSLE. A first questionnaire was constructed including 119 items. To reduce their number, a Delphi analysis was carried out and a second questionnaire with 62 questions was developed. This questionnaire was administered to 139 patients with SLE (58 with NPSLE: 29 active, 29 inactive; and 81 without NPSLE: 39 active, 42 inactive). Questions relevant to the screening of patients were selected on the basis of the receiver operating characteristic (ROC) curve analysis.

Results: Twenty-seven questions concerning central nervous system and psychiatric manifestations were found to be relevant; the remaining could be eliminated without significantly affecting AUC. The area under the ROC curve (AUC) was 0.69 (95% CI 0.61–0.78). A score above 17 was considered as suggestive of the presence of NPSLE with a sensitivity of 92.9% (95% CI 85.1–97.3 %) and specificity of 25.4% (95% CI 14.7–39.00 %).

Conclusions: This questionnaire could represent a 'core set' of questions that could help in clinical practice to identify patients with neuropsychiatric symptoms requiring further evaluation. *Lupus* (2011) **20,** 485–492.

Key words: Clinical practice; neuropsychiatric lupus; questionnaire; screening; systemic lupus erythematosus

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Introduction

Involvement of the nervous system (central, peripheral, or autonomic) has been reported in varying

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frequencies ranging from 14–80% in patients with systemic lupus erythematosus (SLE).[1–14] The ACR case definition for neuropsychiatric (NP) syndromes in SLE represents the most comprehensive attempt to classify clinical manifestations of neuropsychiatric SLE (NPSLE). However, it has been shown that some of the selected clinical symptoms have a low specificity (i.e. headache, mood disorders, mild cognitive dysfunctions).[14–18]

To date there has been little consensus on the role of laboratory, imaging and other diagnostic procedures in the diagnosis and follow-up of patients with NPSLE in routine clinical practice. Furthermore, many interventions are expensive, not readily available in daily practice and may carry considerable risks to patient health.[8,9,19] Recently 'EULAR Recommendations for the Management of Systemic Lupus Erythematosus (SLE) with Neuropsychiatric Manifestations' have been developed, to guide in the assessment of patients with neuropsychiatric involvement.[20] In this respect, the identification of patients less likely to have NPSLE versus those at major risk of having NPSLE by a simple screening questionnaire could simplify clinical practice and help in the decision to refer the patient for further assessment based on these recommendations.

The aim of the present project was the development of a questionnaire administered by physicians that could be useful in identifying patients with SLE and no obvious neuropsychiatric involvement who may be referred for further assessment with the suspicion of NPSLE.

Patients and methods

The development of the questionnaire followed three consecutive phases, namely: (i) items pool development and creation of a first draft questionnaire; (ii) weighting of the variables and items reduction; and (iii) testing on patients and development of the final questionnaire.

Phase I: Items pool development and creation of a draft questionnaire

Based on the ACR case definitions for NP syndromes in SLE, a list of manifestations was prepared. A subsequent literature search identified 41 questionnaires already in use for assessing patients with neurological and psychiatric manifestations similar to those reported in NPSLE (Table 1).[21–59] A first draft questionnaire was then constructed including 119 items that were subdivided into Central Nervous System (CNS), Peripheral Nervous System (PNS) and Psychiatric Manifestations (PsychM). Each possible answer received a score ranging from −1–3.

Phase II: Items reduction and weighting of the variables

The aim of this second phase was to simplify the first draft questionnaire by further reducing the number of questions in order to obtain a pilot version.

A Delphi analysis was carried out among the experts participating in the study. Experts were requested to judge whether each single question should be maintained or excluded. Questions excluded by more than 75% of the experts were removed from the list (16%), questions excluded by less than 50% of the experts were retained (8%); questions excluded by 50–75% of the experts were further discussed and re-evaluated (76%).

The importance of each question was ranked on a Likert scale from 1–3: 1 = irrelevant, non-important; 2 = somewhat relevant, somewhat important; 3 = highly relevant, very important. The mean relevance scores for each item were calculated. Items with a mean rating < 1.5 were removed; items with a mean rating ≥ 1.5 and < 2 had their scores halved; items with a mean rating ≥ 2 and ≤ 2.5 had their scores unchanged; items with a mean rating > 2.5 had their scores doubled.

A pilot version of the questionnaire including 62 questions was developed.

Phase III: Testing on patients and development of the final questionnaire

Each participating centre administered the pilot questionnaire to five SLE patients with active NPSLE, five SLE patients with previously diagnosed inactive NPSLE, five SLE patients with active disease and no history of NPSLE, and finally, five SLE patients with inactive disease and no history of NPSLE. The diagnosis of SLE was based on the 1997 revised ACR classification criteria. The diagnosis of NPSLE was made by the treating physician and represented the gold standard. In addition, global disease activity was also considered based on the ECLAM index: a score above 2 was considered as indicative of active disease, as previously published.[19,20]

The selection of the specific questions relevant to the screening of patients was performed by the receiver operating characteristic (ROC) curve analysis (Prism, Graph Pad Software Inc.) using the area under the curve (AUC) as selection criterion. The area ranges from 0.5 (no accuracy) to 1.0

Table 1 List of the questionnaires used to assess neurological syndromes[21–59]

Acute confusional state	Confusion Assessment Method (CAM)
	Delirium Observation Screening Scale
	Delirium Rating Scale
Acute Inflammatory Demyelinating Polyradiculoneuropathy (Guillain-Barré Syndrome)	No specific questionnaires found
	Questions based on common clinical symptoms
Anxiety disorder	SCL-ANX4
	Liebowitz Self-rated Disability Scale (LSRDS)
	Clinician-Rated Disability Profile (DP)
	Sheehan Disability Scale (SDS)
Aseptic Meningitis	No specific questionnaires found
	Questions based on common clinical symptoms
Autonomic disorder	Autonomic Nervous System Response Inventory (ANSRI)
	Daily Stress Inventory (DSI)
	Somatic Response Survey
	SCOPA-AUT
Cerebrovascular Disease	LOS Angeles Prehospital Stroke Screen (LAPSS)
	The National Institutes of Health Stroke Scale (NIHSS)
Cognitive Dysfunction	Six-Item Screener test
	Mini-Mental State Examination (MMSE)
	Blessed Dementia Scale (BDS)
	The 7-Minute Screen (7MS)
	Questions based on common clinical symptoms
Demyelinating Syndrome	The MS Symptom and Impact Diary (MSSID)
	The three-item ID Migraine
Headache	
	3-Question Headache Screen
	Headache Disability Inventory (HDI)
	Headache Impact Test (HIT)
	Migraine Disability Assessment Score (MIDAS)
	Migraine Specific Questionnaire (MSQ)
	Migraine Therapy Assessment Questionnaire (MTAQ)
	Headache Needs Assessment Survey (HANA)
	Migraine Assessment of current Therapy (Migraine –ACT)
	Pain Experience Instrument- Headache Version (CPEI-HA)
Mononeuropathy (single/multiplex)	Questions based on common clinical symptoms
	Neuropathic Pain Questionnaire (NPQ)
	Neuropathic Pain Scale (NPS)
	Leeds Assessment of Neuropathic Symptoms and Signs (LANSS)
	Self-report Leeds Assessment of Neuropathic Symptoms and Signs (S-LANSS)
Mood Disorders	Depression screening with SIG and CAPS and with SALSA
	Hamilton Rating Scale for Depression (HRSD)
Movement Disorder (Chorea)	Unified Huntington's Disease Rating Scale (UHDRS)
Myasthenia Gravis	Myasthenia Gravis Questionnaire (MGQ)
Myelopathy	Questions based on common clinical symptoms
Neuropathy, Cranial	Questions based on common clinical symptoms
Plexopathy	Questions based on common clinical symptoms
Polyneuropathy	Neuropathy Symptom Score
Psychosis	Questions based on common clinical symptoms
Seizures and Seizure Disorders	VA Seizures Frequency and Severity Scale (VA)
	National Hospital Seizure Severity Scale (NHS3)
	Occupational Hazard Scale
	Liverpool Seizure Severity Scale Items
	Hague Seizure Severity Scale

(perfect accuracy). This method has the advantage of synthesizing information on the sensitivity and specificity for detecting improvement by an external criterion. Cut-off values to separate patients were established in order to maintain a high sensitivity (>90%) and a specificity of at least 20%.

Results

Out of the initial 119 questions, 65 were maintained after the first Delphi round. Based on the mean relevance scores for each item, three additional questions were excluded. Of the remaining 62, 21 had

their scores halved, 35 had their scores unchanged and five had their scores doubled. These 62 questions constituted the pilot questionnaire.

In total, 139 SLE patients from 11 different European Centres (five in Italy, two in Spain, one in Lithuania, one in Poland, one in Portugal, one in The Netherlands) were enrolled in the study. Based on the NPSLE status, patients were distributed as follows: 58 patients with NPSLE, 29 active and 29 inactive at the time of investigation; 81 patients without history of NPSLE, 39 with active disease and 42 with inactive disease. Of NPSLE patients, 74% presented with CNS involvement (most frequently with vascular disease 38%, epilepsy 21%, and headache 9%) 21% PsychM, and 5% PNS manifestations. PNS questions showed minimal predictive power for NPSLE, and therefore were excluded from the questionnaire.

In total, 27 questions from the CNS (12) and PsychM (15) groups were found to be relevant, while the remaining could be removed without significantly affecting the AUC of ROC curve (Figure 1). The final AUC was 0.69 (95% CI 0.61–0.78). The questionnaire is reported in Table 2.

Table 2 Questionnaire

CENTRAL NERVOUS SYSTEM	
Headache	
1. Do you frequently suffer from headaches (more than 1 episode every month?)	
Yes	0.5
No	0
2. If YES	
When did these headaches begin?	
Before the onset of SLE	-1
Before the onset of SLE, but worsening after	0
After SLE onset	1
3. Does your headache improve after taking your daily dose of corticosteroids?	
Never	0
Sometimes	1
Often	2
Always	3
Cerebrovascular Disease, TIA	
4. Have you had (in the last 3 months), without warning, a sudden loss of the power or of sensation of an arm or of a leg?	
Never	0
Yes, 1 episode	2
Yes, 2 episodes	4
Yes, more than 2 episodes	6
5. Have you been (in the last 3 months), without warning, suddenly unable to speak properly for less than 24 hours?	
Never	0
Yes, 1 episode	2
Yes, 2 episodes	4
Yes, more than 2 episodes	6
Demyelinating syndrome	
6. In the last 3 months have you had weakness or heaviness in your arms or legs?	
Never	0
Yes, rarely	1
Yes, often	2
Yes, always	3
7. In the last 3 months have you had unsteadiness or loss of balance?	
Never	0
Yes, rarely	1
Yes, often	2
Yes, always	3
8. In the last 3 months have you had alteration or loss of sensation (e.g. numbness, tingling, pins and needles) in some areas of your body?	
Never	0
Yes, rarely	1
Yes, often	2
Yes, always	3
9. In the last 3 months have you had blurred, double or shaky vision?	
Never	0
Yes, rarely	2
Yes, often	4
Yes, always	6
Seizures	
10. Do you suffer from seizures?	
Yes	2
No	0
I don't know	0
Movement Disorder- Chorea	
11. Have you had in the last 3 months abrupt, purposeless, nonrhythmic involuntary movements?	
Never	0
Yes, rarely	1
Yes, often	2
Yes, always	3
Aseptic Meningitis	
12. In the last 3 months have you had acute or gradual onset of headache with sensitivity to light, neck stiffness, confusion and fever?	
Never	0
Some time	0.5
Most of the time	1
All of the time	1.5
PSYCHIATRIC MANIFESTATIONS	
Acute Confusional State and Cognitive dysfunctions	
13. In the last 3 months, have you had difficulties in concentrating for a long time on the activities that you are doing?	
Never	0
Sometimes	0.5
Most of times	1
Always	1.5
14. In the last 3 months, have you had difficulties in planning and managing your daily tasks or in organizing new activities?	
Never	0
Sometimes	1
Most of times	2
Always	3
15. In the last 3 months, have you had any problems in remembering or recalling faces, routes, images?	
Never	0
Sometimes	1
Most of time	2
Always	3
Mood Disorders	
16. In the last 3 months, have you had sleep disturbances (insomnia with 2-4 am awakening)?	
None of the time	0

Table 2 Continued

CENTRAL NERVOUS SYSTEM	
Some time	0.5
Most of the time	1
All of the time	1.5
17. In the last 3 months, have you had decreased interest in activities (anhedonia)?	
None of the time	0
Some time	0.5
Most of the time	1
All of the time	1.5
18. In the last 3 months, have you felt depressed?	
Ever	0
Sometimes	1
Often	2
Always	3
19. In the last 3 months, have you had suicidal thoughts?	
None of the time	0
Some time	1
Most of the time	2
All of the time	3
Anxiety Disorder	
20. In the last 3 months, have you felt more nervous and anxious than usual?	
None of the time	0
Some time	0.5
Most of the time	1
All of the time	1.5
21. In the last 3 months, have you felt afraid for no reason at all?	
None of the time	0
Some time	0.5
Most of the time	1
All of the time	1.5
Psychosis	
22. In the last 3 months, have your relatives told you that you act in bizarre and inappropriate ways?	
None of the time	0
Some time	1
Most of the time	2
All of the time	3
23. In the last 3 months, have you felt that you have more than one identity?	
None of the time	0
Some time	1
Most of the time	2
All of the time	3
24. In the last 3 months, have you frequently repeated the same activities?	
None of the time	0
Some time	0.5
Most of the time	1
All of the time	1.5
25. In the last 3 months, have you had impulsive unpredictable behaviour?	
None of the time	0
Some time	1
Most of the time	2
All of the time	3
26. In the last 3 months, have you heard voices giving you orders/do you have hallucinations?	
None of the time	0
Some time	1
Most of the time	2
All of the time	3
27. In the last 3 months, have you thought of being persecuted?	
None of the time	0
Some time	1
Most of the time	2
All of the time	3

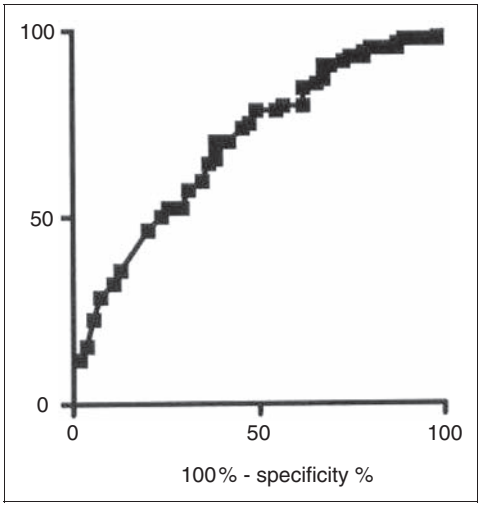

Figure 1 ROC Curve. A threshold of 17 points in the questionnaire score is able to distinguish a positive patient, with a sensitivity of 92.9% (95% CI 85.1–97.3 %) and a specificity of 25.4% (95% CI 14.7–39.00 %).

The best discriminating cut-off point corresponded to a score of 17 (i.e. a score higher than 17 to define a positive patient), for a sensitivity of 93% (95% CI 85.1–97.3%) and specificity of 25% (95% CI 14.7–39.0%). If CNS and PsychM were considered separately, the cut-off values identified to define positive patients were found to be 9 (sensitivity 90.6%, specificity 23.3%) and 10 (sensitivity 91.3%, specificity 25.00%) respectively.

Discussion

NP manifestations in SLE are very diverse and difficult to be evaluated; EULAR recommendations for monitoring NPSLE have been recently developed that offer a feasible guide in patient assessment. However, in routine clinical practice, patient screening for the presence of NPSLE is mainly based on a focused history, and patients are referred for further assessments according to the judgement of the treating physician. This leads to variability, as mild to moderate symptoms may be overlooked, depending on the physician's experience.

In the present study, we developed a simple questionnaire to screen patients with SLE for NP manifestations in routine clinical practice. This questionnaire should offer the treating physician a validated framework that supports the clinical examination, offering a core set of questions able to identify patients who should be referred for further assessment.

The questionnaire includes 27 items covering CNS involvement and PsychM. Items referring to PNS manifestations turned out to be not relevant and were therefore excluded. A score above 17 was found to be suggestive of the presence of NP involvement and represents the cut-off value to refer patients for further assessment. This cut-off value offers a high sensitivity but a low specificity. However, since the aim of this questionnaire was to offer a first-level screening procedure, and by no means a tool for diagnosing such a complex condition as NPSLE, we have decided that the actual working point should be biased in favour of sensitivity.

The major objection raised by such an approach is the low specificity, leading to a high number of false-positive patients referred to the specialists. In fact, non-specific symptoms occurring in association (e.g. subjective complaint of cognitive impairment, low mood, headache), might score higher than more severe manifestations (e.g. seizures) when occurring alone. Although no corrections were made in the attribution of the scoring values, the final score was attributed on the basis of the panellists judgement on the relative importance of each question.

This questionnaire was developed to offer a simple screening tool to improve physician awareness of the presence of NP symptoms and should represent a guide in patient assessment in routine clinical practice. It is not intended to replace standard NP assessment of the patient with SLE. As in the case of any new neurological complaint, a positive screening result should be just a signal to the treating physician, who should evaluate the findings and draw the necessary conclusions.

At the opposite end of the spectrum, scores below the cut-off value that could be associated with a low suspicion of NPSLE should cautiously be judged by the treating physician.

Nonetheless, any screening questionnaire may help the physician in the assessment of patients, eventually reducing the unwanted variability. Such questionnaires need to be simple to administer and complete, and need to be acceptable to respondents. Short questionnaires minimize a patient's time and effort, and thus increase a patient's willingness to complete the questionnaire. To our knowledge, this is the first attempt to develop a simple questionnaire to screen patients for the presence of NPSLE to be used in clinical practice.

The absence of items referring to the presence of PNS involvement may be viewed as another limitation of this questionnaire. However, this reflects the relatively low prevalence of PNS involvement among patients with SLE.

Although the questionnaire was developed to be administered by the physician during assessment of the patient, in view of its simplicity it will also be tested as a patient-administered questionnaire.

In conclusion, this simple questionnaire may assist the treating physician in the screening of patients with SLE for the presence of non-overt NP involvement and provide a first-level evaluation before deciding on additional testing. This may avoid the delay in diagnosis and treatment.

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Conflict of interest

The authors declare that they have no conflicts of interest.

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