Neuropsychiatric questionnaires in systemic lupus erythematosus

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ABSTRACT

Patients with systemic lupus erythematosus (SLE) can be affected by a multitude of neurologic and psychiatric symptoms with a wide range of prevalence and severity. Irrespectively from attribution to SLE or other causes, neuropsychiatric (NP) symptoms strongly impact short-term and long-term outcomes, thus NP evaluation during routine clinical practice in SLE should be undertaken regularly.

The assessment of NP involvement in SLE patients is challenging and the available diagnostic tools fail to guarantee optimal diagnostic accuracy, sensitivity to changes as well as feasibility in routine clinical care.

Standardised questionnaires (both physician-administered and self-reported) can offer valuable help to the treating physician to capture all possible NP syndromes; few SLE-specific NP questionnaire have been developed but validation in large cohort or cross-cultural adaptations are still pending. On the other hand, general instruments have been largely applied to SLE patients.

Both kinds of questionnaires can address all possible NP manifestations either globally or, more frequently, focus on specific NP symptoms. These latter have been mainly used in SLE to detect and classify mild and subtle symptoms, more likely to be overlooked during routine clinical assessment such as headache, cognitive impairment and psychiatric manifestations.

In conclusion, this literature review highlights a clear case for validation studies in this area and the wider implementation of questionnaires to assess NP involvement is still warranted. The broader use of such instruments could have important consequences; first of all, by standardising symptom assessment, a better definition of the prevalence of NP manifestation across different centres could be achieved. Secondly, prospective studies could allow for the evaluation of clinical significance of mild symptoms and their impact on the patient's function and quality of life.

Introduction

Patients with systemic lupus erythematosus (SLE) may present a wide spectrum of neurological and psychiatric symptoms of a variable degree of severity. Despite some advances in understanding the general disease pathogenesis, neuropsychiatric SLE (NPSLE) remains a clinical challenge for the treating physician, both from a diagnostic and a therapeutic perspective (1-4).

NP manifestations in SLE range from common clinical symptoms such as headache, mood disorders, and cognitive complaints, to less frequent manifestations such as psychosis, myelopathy, and peripheral neuropathies. There is considerable uncertainty surrounding several issues, including the true prevalence of neuropsychiatric (NP) events, their attribution to SLE or to other causes, and their clinical significance.

In this review we summarise the available evidence concerning the assessment of neuropsychiatric symptoms in SLE patients, with a special focus on tools for routine clinical care and long-term observational studies.

Why do we need to assess neuropsychiatric symptoms in SLE patients?

Neuropsychiatric assessment during routine clinical practice in SLE should be undertaken regularly. Its importance is highlighted in the following framework.

First of all, NP symptoms are common in SLE; estimates of prevalence have ranged from 14% to more than 90%, depending on case definitions and patient selection (1-3). However, only a minor-

ity of NP events in SLE is attributed to the disease itself (from 17 to 30% and, approximately depending upon the stringency of the attribution rules). No significant differences in impact on patient status between NP events attributed to SLE or not attributed to SLE have been reported, emphasising the importance of including all NP events in clinical studies of NPSLE. Moreover, the presence of NP symptoms is associated with a poor prognosis, damage accrual, reduced quality of life, and work disability. The presence of NP events, regardless of their attribution to SLE or to non-SLE causes, is associated with a significant negative effect on health-related quality of life (4-5).

Literature data on mortality are somewhat contrasting but recent studies have shown an increased mortality rate compared to the general population and to SLE patients without NP involvement (6-8).

Secondly, NP symptoms may be present early after disease onset in up to 40% of the patients; in inception cohort studies, patients continue to accrue new NP events over time, attributed to both SLE and non-SLE causes. Nonetheless, the highest proportion of NP events attributed to SLE occurs early during the disease course, and it could be hypothesised that a therapeutic intervention at this time might be associated with a better prognosis. In this context, a therapeutic window of opportunity for immunosuppressive therapies has been suggested, further underscoring the need for NP assessment in routine SLE care (9, 10).

Assessment tools for neuropsychiatric manifestations in SLE

The wide range of possible NP manifestations, as well as the lack of accurate diagnostic biomarkers render the assessment of NP involvement in SLE a continuous challenge (11).

The availability of standardised questionnaires provides significant value as a practical tool to collect information from individuals in a cost-effective manner; in addition to providing a cost-effective research tool for use in data collection, patient self-report questionnaires present invaluable information for the attending physician in routine clinical care. The availability of a validated questionnaire may help the patient prepare for the encounter with the doctor, and help the physician significantly in formulating clinical decisions, while the patient does most of the work (12-14).

To date, few questionnaires have been specifically developed to assess NP involvement in SLE but several non SLE-specific tools that have been also tested in SLE patients. They address all possible NP manifestations either globally or, more frequently, focus on specific NP symptoms.

The first type of questionnaire has the advantage of providing a comprehensive evaluation of the patient in a short timeframe, thus allowing for triage of potential candidates for further and more faithful assessments. On the other hand, questionnaires focusing uniquely on single NP symptoms can reflect diagnostic/classification accuracy but are time consuming and only applicable to selected cases in routine clinical practice.

"Global" NP questionnaires

In 2003, Denburg *et al*. developed a 42- item self-administered neuropsychiatric questionnaire including a range of NP-related symptoms and excluding major NP events. The NP-Q symptoms were divided into 26 neurologic, 13 psychiatric, and 6 cognitive items. The intent was to collect reasonably exhaustive information systematically and rapidly, and in order to possibly alert the physician about the need for further investigations, but not as a replacement for diagnostic purposes. They applied the questionnaire to 76 patients without overt NP syndromes, and found a significant association between higher item endorsement and lower cognitive function as well as significantly poorer cognitive performance in the high compared to low endorser groups. These findings suggested that even "minor" NP symptoms might raise the suspicion of subclinical NP involvement in the absence of clinically evident NPSLE (15).

In 2010, with the same screening objective, Mosca *et al*. developed a physician-administered questionnaire to screen patients with SLE for the presence of symptoms suggestive of NP involvement in clinical practice, based on the ACR case definitions for NP syndromes in SLE. The questionnaire is composed of 27 weighted questions covering central nervous system (CNS) and psychiatric (Psyc) items, and was developed on the basis of a literature search and expert opinion consensus.

In total, 139 SLE patients from 11 different European Centres were tested including 58 patients with recognised NPSLE and 81 patients without a history of NPSLE. ROC analysis showed the best discriminating cut-off point corresponded to a score of 17; this cut-off value offers a high sensitivity but a low specificity, in accordance with the aim of the questionnaire, namely for use as a first-level screening procedure. For the same reason, when CNS and Psych items were considered separately, the cut-off values identified to define positive patients were found to be 9 and 10, respectively. This questionnaire has the advantage of being simple to administer, complete in its cover of a wide range of manifestations and acceptable by physicians and patients because it minimises time and effort in comparison with previous forms of evaluation (16). Indeed, 5 to 10 minutes are required to be administered by a physician without specific training (personal, unpublished data). The questionnaire is regularly in use at the authors' centres, being administered to all SLE outpatients before the formal visit. External validations are currently ongoing.

The Adult Psychiatric Morbidity Questionnaire (APMQ), is a Brazilian screening instrument designed by Santana *et al*. to identify psychiatric morbidity in the general population. The validity and reliability of the QMPA have been established in several community-based studies providing at a cutoff point of 7, a sensitivity of 83% and a specificity of 71% (17).

In 2013, Beltrao *et al*. used the APMQ in the evaluation of psychiatric symptoms in a sample of 72 SLE patients, finding a higher frequency of abnormal APMQ (89%) mainly due to common mental disorders such as anxiety, so-

matisation, irritability, depression (60 patients, 93.7%), while only 4 patients were classified (6.3%) as having psychosis (18).

With different purposes, The Mini International Neuropsychiatric Interview (M.I.N.I. 6.0) is a short structured diagnostic interview for psychiatric disorders. With an administration time of approximately 15 minutes, the M.I.N.I. 6.0 is the structured psychiatric interview of choice for psychiatric evaluation and outcome tracking in clinical trials and epidemiological studies (19). In SLE this instrument was used by Jarpa *et al*. who applied the interview to 83 consecutive non-selected Chilean patients with SLE, finding a 44.6% prevalence of psychiatric diagnoses, the most frequent of which was a major depressive episode which occurred in 21.7% (20).

"Symptoms-specific" questionnaires

Disease-specific questionnaires have not been developed to assess single NP symptoms in SLE patients, but instruments developed and validated in general setting or other diseases have been widely applied in SLE. Among the several possible NP symptoms in SLE, questionnaires have been mainly used to detect and classify mild and subtle symptoms, more likely to be overlooked during routine clinical assessment.

Headache

Headache is a frequent complaint in SLE patients, being reported in up to 72% of the patients; however, because it is not present more frequently in SLE patients than in the general population, its association with the underlying disease is still controversial (21-24).

Indeed, the term "lupus headache" implies a unique form of headache that is rare (1.5%) and directly attributable to SLE. It represents a stand-alone item with similar definitions in the SLEDAI-2K score (which defines lupus headache as a severe, persistent headache that may be migrainous, but must be non-responsive to narcotic analgesia) and the British Isles Lupus Assessment Group (BILAG) 2004 index, (which defines lupus headache as a disabling headache that is unresponsive to narcotic analgesia and lasts ≥3 days) (25, 26). Headache is included in the ACR case definitions criteria and it is defined according to the International Headache Society (IHS) classification in 5 subsets (migraine with and without aura, tension headache, cluster headache, headache from intracranial hypertension, and intractable non-specific headache) (2, 27).

In 2001, 414 SLE patients were evaluated for headache with the University of California, San Diego (UCSD) Migraine Questionnaire, based on the IHS criteria to classify headache syndromes; headaches were reported in 62% of patients and 39% met diagnostic criteria for migraine (28, 29).

Recently, Tjensvoll *et al*. administered the Headache Impact Test-6 (HIT-6) and the Migraine Disability Assessment (MIDAS) questionnaires to evaluate headache-related disability in a sample of 77 SLE patients in comparison with healthy subject and patients suffering from Sjögren's syndrome. The authors reported that patients have more severe headaches than healthy subjects a higher disability burden from headaches (30).

Cognitive impairment

Cognitive impairment (CI) is one of the more common NP symptoms in SLE, reported in up to 80% of the cases. Symptoms include cognitive slowing, decreased attention, impaired memory, and decision-making impairment (*e.g*. difficulty with multitasking, organisation, and planning).

The frequent subtle and subclinical nature of CI as well as its intermittent and unpredictable expression, often occurring irrespectively of global SLE disease activity, marks the assessment of these symptoms as a diagnostic challenge (31-36).

So far, several CI instruments have been applied to SLE patients and their characteristics are reported in Table I.

The comprehensive 4-hour neuropsychological battery administered by an expert neuropsychologist represents the *gold standard* for objective CI assessment. In 1999, the ACR Committee for nomenclature and case definitions in NPSLE suggested a 1-hour test battery with demonstrated acceptable agreement (90%) with formal neuropsychological tests and adequate reliability, suggesting its potential usefulness to identify SLE patients with CI (37).

To save time and standardise the procedure for non-expert administration, computer-based and audiotape-based instruments have also been tested in SLE (ANAM, PASAT) with good diagnostic accuracy. For instance, the ANAM battery takes 30–45 min to administer and includes a variety of tasks designed to assess neurocognitive efficiency through measures of response time and accuracy (38).

The Cognitive Symptom Inventory (CSI) score was proposed in 2002 in order to overcome the limits of time and resources consumed by current objective evaluations of CI. This consisted of a rapid screening questionnaire consisting of a 21-item self-report measure of cognitive function, with the objective of screening patients necessitating formal CI assessment (39). However, in a validation study by Hanly *et al*. in 2012, no significant association between CSI scores and objective performance on a computer-administered neuropsychological test battery (ANAM) were observed; instead, cognitive complaints of patients with SLE were associated with self-reported symptoms of anxiety and depression (40).

Anxiety and depression

Psychiatric manifestations are fairly common in SLE patients, occurring in up to 75% of cases. Among these, depression and anxiety are among the most frequent disorders observed. Studies cite a broad range of prevalence rates of depression ranging from 17 to 75%, a much higher frequency than in the general population (18, 20, 41). According to the Diagnostic and Statistical Manual of Mental Disorders-DSM-5 edition, mood and anxiety disorders should be diagnosed using the Structured Clinical Interview for DSM Disorders (SCID) 2014 (42). These disorders can also be evaluated by depression, anxiety and/or stress and personality scales. There is no agreement concerning an optimal method to evaluate psychiatric symp-

Table I. Tests used to assess cognitive impairment in SLE.

Patients *Author, year* *Study design;* *Number of patients*	Test used to asses CI in SLE	Feasibility *-1. time required* *-2. comprehensibility* *-3. Special technology* *-4. Costs*
Carlomagno S, 2000 LOS 51	*MDB* (Mental Deterioration Battery)	-1: 1 hour -2 :expert psychometrist -3 : no -4: N.A.
Alarcòn GS, 2002 Cross-sectional 156	*CSI* (Cognitive Symptoms Inventory)	-1: 10 minutes -2 self administered with limited assistance -3 No -4 N.A.
Denburg SD, 2003 LOS 30	*42-ITEMS*, *25-ITEMS*, *8- ITEMS* *NP-questionnaire*	-1 N.A. -2 self administered -3: NA -4 N.A.
Holliday SL, 2003 Cross-sectional 67	*ANAM* (Automated Neuropsychological Assessment Metrics)	-1 N.A. -2 N.A -3 Personal Computer -4 N.A.
Shucard JL, 2004 Cross-sectional 45	*PASAT* (Paced Auditory Serial Addition Test): processing speed and working memory	-1 N.A. -2 :Yes -3 Audiotape -4 N.A.
Kozora E,2004 Cross-sectional 52	*ACR neuropsychological battery*	1.1 hour 2.administered by technicians trained 3.No 4.N.A.
Roebuck-Spencer TM, 2006 Cross-sectional 60	*ANAM* (Automated Neuropsychological Assessment Metrics)	1.30 minutes 2.self administered 3.Personal computer 4.NA

toms in SLE. Indeed, differences in assessment techniques appear to be the main explanation for the variability in findings and important methodological limitations are present in the available literature, preventing accurate descriptions of the prevalence of depression and anxiety disorders in SLE. Moreover, it should be taken into account that the validity of the data reported by patients may not necessarily be generalised to all contests. This limit has been well described in rheumatoid arthritis (RA) when evaluating patients for depression and other psychological tendencies with questionnaires developed in the general population; indeed, in RA patients, the presence of somatic symptoms can be responsible of *false positive* answers to questions that in the general population can suggest psychological complains. This aspect, named "criterion contamination" should be considered when applying general instruments to specific patients groups (43, 44).

A summary of the studies and relevant instruments used in the evaluation of depression in SLE have been recently reviewed by our group (45). The Beck Depression Inventory (BDI) is one of the most widely used instruments for measuring the severity of depression in the general population and in SLE patients. BDI is a 21-question inventory for self-assessment of depressive symptoms present in the month prior to evaluation. According to the BDI authors' recommendations, a BDI score greater than 10 is indicative of depressive symptoms, while clinically significant depression is defined when the BDI score is higher than 10 (46).

Recently, van Exel *et al*. used the BDI questionnaire to estimate the prevalence of depression in 102 SLE patients; they found a higher BDI score in SLE subjects, corresponding to a depression prevalence of 16.6% *versus* 6.7% in the general population. Interestingly only 7% of SLE subjects with high BDI scores used antidepressants, suggesting inadequate recognition and treatment of depression in SLE (47).

The Self-rating Anxiety Scale (SAS) is one of the most widely used instruments for measuring anxiety; it is a 20-item self-report assessment scale and each question is scored on a Likert-type scale of 1–4. The presence of clinically relevant anxiety symptoms is defined by SAS scores >44 (48). The State Trait Anxiety Index Y2 (STAI-Y2) is one of the most widely used instruments for measuring trait anxiety. STAI-Y2 is a 40-item scale which evaluates relatively stable aspects of *anxiety proneness*, including general states of calmness, confidence, and security. Item scores are added to obtain a possible range of scores of 20–80, higher scores indicating greater anxiety (49). Both have been used in SLE cohorts (41, 50, 51).

Conclusion

NP assessment in SLE is a continuous challenge both for clinical and research purposes.

This review highlights how the use of a standardised clinical interview by questionnaires is important in recognising neuropsychiatric symptoms in SLE patients. These, even if subtle and mild, could otherwise be overlooked during routine clinical assessment.

Indeed, physician and patient-administered questionnaires represent a fundamental tool to standardise evaluation, early detection of symptoms and quantification of the severity and progress of a particular manifestation.

So far, few instruments have been developed to specifically asses NP symptoms in SLE. The limits of these instruments are that they have not yet been validated in larger and independent SLE cohorts and that they can depict NP symptoms but their ability in symptoms attribution to SLE or to other

causes remains to be clarified. On the other hand, many instruments validated for the general population have been also applied to SLE patients but the reliability of these measures in such a specific population remains to be evaluated. Indeed, it is well known that the population in which a questionnaire has been validated may be different from our study population, and prudence must be used in interpreting the data.

There is therefore a clear case for validation studies in this area and their wider implementation is still warranted. The broader use of such instruments could have important consequences; first of all, by standardising symptom assessment, a better definition of the prevalence of NP manifestation across different centres could be achieved. Secondly, prospective studies could allow for the evaluation of clinical significance of mild symptoms and their impact on the patient's function and quality of life. Indeed, literature data suggest that the assessment of NP symptoms by structured questionnaires, especially if self-administered, is able to pick up subjective and shadowy complaints that significantly contribute to the disease burden, irrespectively of clinical attribution; however, these symptoms are usually neglected by the physician-driven routine assessment. By including the patient's perspective, a more exhaustive estimation of the NP picture could be accomplished, with important therapeutic and prognostic consequences.

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