Evaluation of central nervous system involvement in SLE patients. Screening psychiatric manifestations – a systematic review

Vargas JV[1], Vaz CJ[2]

ABSTRACT

Cognitive dysfunction, mood and anxiety disorders are three out of the five psychiatric manifestations included the description of neuropsychiatric Systemic Lupus Erythematosus (SLE). These manifestations are among the most prevalent in SLE having an important impact on patients quality of life. However, the unknown etiology allied to the lack of clarity on the best diagnosis procedure, makes early diagnosis dificult. This manuscript reviews the recent literature on the screening instruments focused on identifying lupus patients with probable psychiatric manifestations.

Keywords: Neuropsychiatric lupus; Screening; Cognitive dysfunction; Mood disorders; Anxiety disorders.

INTRODUCTION

Systemic Lupus Erythematosus (SLE) is a chronic, inflammatory, autoimmune disease characterized by its multi-systemic involvement and multiple clinical manifestations. It can involve the nervous system on its central or peripheral components.

In an effort to standardize nomenclature and diagnostic methodology, the American College of Rheumatology Ad Hoc Committee on Neuropsychiatric Lupus, published in 1999, the case definitions and diagnostic recommendations on Neuropsychiatric Lupus (NPSLE). Nineteen syndromes were included in NPSLE and for each were suggested not only the

1. 6th year Medical Student of the Master Degree in Medicine Course of the Faculty of Medicine of the University of Porto
2. Assistent Professor of Rheumatology of the Faculty of Medicine of the University of Porto and Attending Physician of Rheumatology of São João Hospital, Porto

diagnostic criteria and testing but also associations and exclusions[1]. The publication was widely accepted and has been used ever since in the study of NPSLE in adult and pediatric populations.

Recent studies report a prevalence of neuropsychiatric manifestations of 27-80% in adults[2-8], and 22-95% in children[9-12]. NPSLE can develop in any time during the course of the disease but there are several studies reporting a tendency to occur early in its course[5,8]. Furthermore, association between neuropsychiatric events and disease activity has been reported in some studies[13,14] and denied in others[15-19].

Five out of 19 syndromes included in NPSLE are psychiatric and were considered by the ACR Ad Hoc Committee on NPSLE according to the DSM-IV diagnostic criteria: mood disorders, anxiety disorders, cognitive dysfunction, psychosis and acute confusional state.

The importance of studying psychiatric phenomena in lupus disease lies not only in its high prevalence reported[20] but mainly in what it represents clinically and socioeconomically. Psychiatric manifestations have been associated with a decreased quality of life[5,8,19], increased functional disability[3], sleep disorders[21,22], increased unemployment rate[23,34] and health service utilization[25,26].

There is still little consensus on the role of laboratory tests and imaging techniques in the diagnosis of psychiatric syndromes and due to the lack of simple diagnosis process, psychiatric syndromes are frequently undiagnosed.

This manuscript pretends to a be systematic review on the recent literature focused in the study of screening tools for the identification of SLE patients with probable cognitive dysfunction, mood disorders or anxiety disorders, the three most prevalent psychiatric manifestations in lupus.

METHODS

A Pubmed/Medline and Scopus search was conducted from January 2002 to January 2012 using the following keywords: "neuropsychiatric lupus" or "systemic lupus erythematosus" combined with "diagnosis", "anxiety disorders", "mood disorders" and "cognitive dysfunction". A follow-up of the relevant bibliography in articles was also done in order to identify additional relevant studies.

Abstracts of all identified studies were reviewed by two investigators. Every time an abstract was considered as potentially relevant, by either or both investigators, the full-text was retrieved and reviewed for relevance by applying the exclusion and inclusion criteria.

All articles investigating a screening method or tool for the diagnosis of psychiatric lupus were included.

Review articles, case reports, studies in languages other than english or portuguese were immediately excluded. Studies that did not relate with diagnosis of psychiatric manifestations in the lupus setting or with its laboratory and/or imaging diagnosis were also excluded.

RESULTS

The described search identified 446 articles (Figure 1), of which 102 were considered as potentially relevant. Forty-seven articles were excluded based on abstract analysis. The remaining 55 studies were reviewed on its full text and the inclusion and exclusion criteria were applied. Twelve studies were included in this systematic review.

Table I summarizes the main methodologic characteristics and results of the included studies

COGNITIVE DYSFUNCTION

Difficulties in remembering, concentrating and performing cognitive-dependent activities are frequent complaints of SLE patients[27,28]. In fact, Cognitive Dysfunction (CD) has been reported as one of the most frequent neuropsychiatric manifestations in SLE, having a prevalence in the adult population of 5,4- -50%[5,6,14,16,28-33] and in the pediatric population of 7,3- -79,8%[5,6,14,19,29,30].

In adults, CD increases the risk of physical injury, reduces patients ability to properly adhere to treatment regimens and to function effectively in their home and work environments[17]. In pediatric patients cognitive
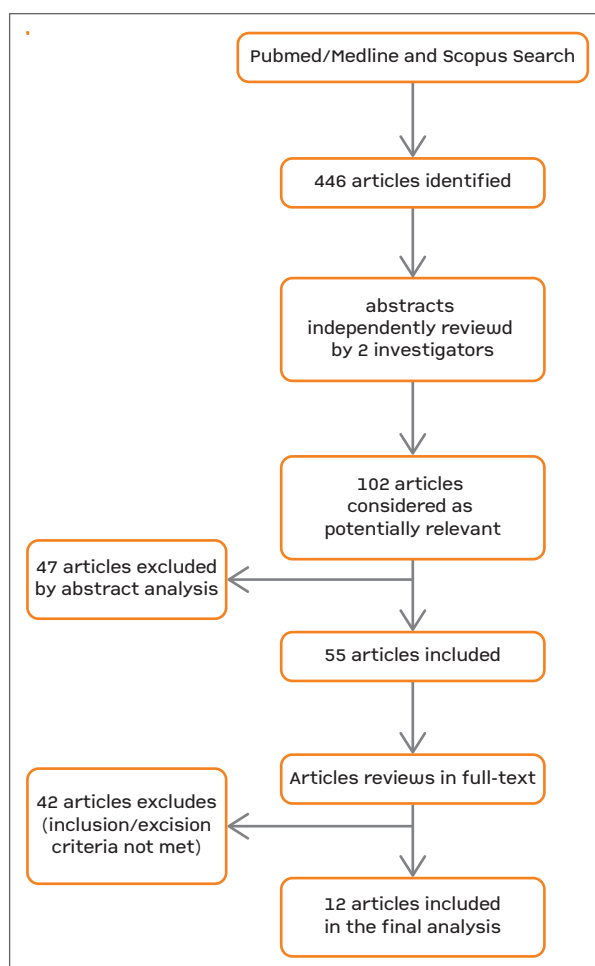
FIGURE 1. Flowchart showing research process

impairment may prevent the normal development, with serious repercussions throughout life[34].

A comprehensive battery of neuropsychological tests is the ideal method to evaluate the presence and severity of cognitive dysfunction. However, in order to facilitate the diagnosis process, the ACR Ad Hoc Committee on NPSLE proposes an one-hour battery of brief mental status examinations (short ACR-SLE battery)[1].

The short ACR-SLE battery has been validated and found reliable in spite of high practice-effect observed in some tests by a study that tested the correlation between the short ACR-SLE battery and a comprehensive neuropsychological battery[35]. Nevertheless the short ACR-SLE battery is not easily available, requires administration by specialized professionals and is too expensive to be used in routine clinical consults[15,27,28].

The ANAM is a, 30 to 45 minutes self-administered,

TABLE I. SUMMARY OF MOST RELEVANT METHODOLOGIC TOPICS AND RESULTS OF INCLUDED STUDIES

	Study Design (data collection)	Neuropsychiatric syndrome	Screening Measure	Diagnostic/ Verification Measure(s)	No. of SLE patients	Control patients	Frequency of affected	Results Psychometric properties	Results Relevant points
Holliday et al[27] (2003)	Cross-sectional study (prospective)	Cognitive dysfunction	ANAM	Formal NP testing	67	–	CD = 79%	–	Age + ANAM scores regression model accounts for 61 % of variance observed on formal NP tests
Roebuck-Spencer et al[36] (2006)	Cross-sectional study (prospective)	Cognitive dysfunction	ANAM	Formal NP testing	60	–	–	Sn = 76,2% Sp = 82,8%	ANAM's mood scale correlates with BDI-II
Hanly et al[31] (2010)	Case-control study (prospective)	Cognitive dysfunction	ANAM	–	68	RA = 33 MS = 20 H = 29	CD in SLE = 11-50% CD in RA = 9-61% CD in MS = 20-75%	–	No statisticaly significant diference in impairment rate between SLE and RA patients
Brunner et al[15] (2007)	Cross-sectional study (prospective)	Cognitive dysfunction	Ped-ANAM	Formal NP testing	27 (pediatric)	–	CD = 59%	–	Correlations were found between Ped-ANAM scores and performance in formal NP tests
Alarcon et al[17] (2002)	Cross-sectional study (prospective)	Cognitive dysfunction	CSI	SLAM, SDI, SF-36,Pain Visual-Analog scale	156	–	–	–	Correlations were found between CSI and the validated measures of cognitive dysfunction
Adhikari et al[32] (2011)	Case-control study (prospective)	Cognitive dysfunction	MoCA	ANAM	44	Age, sex and race-matched RA patients	CD in SLE = 25%	Sn = 83% Sp = 73% PPV = 50% NPV = 92%	MoCA classified 29,5% as cognitively impaired in the SLE group
Kozora et al[37] (2008)	Case-control study (prospective)	Cognitive dysfunction	NRS	Formal NP testing	67	H =29	CD in SLE = 20,9%	–	"mentation and mood" parameter accounted for the difference between the SLE and control groups
Julian et al[28] (2011)	Cross-sectional study (prospective)	Cognitive dysfunction	Telephone PDQ	Formal NP testing	138	–	CD = 27 %	Sn = 77% Sp= 65% PPV = 43% NPV = 94%	67% of patients were correctly classified as cognitively impaired Confounded by sociodemograpfic variables and depression

(*continues on the next page*)

SLE= Systemic Lupus Erythematosus; H = Healthy; RA = Rheumatoid Arthritis; MS = Multiple Sclerosis CD = Cognitive dysfunction; Sn= Sensitivity; Sp= Specificity; PPV= Positive predictive value; NPV= Negative predictive value; ANAM = Automated Neuropsychological Assessment Metrics; Formal NP testing = Representative neuropsychological test battery derived from the ACR recommendations[1]; Ped-ANAM = Pediatric Automated Neuropsychological Assessment Metrics; CSI = Cognitive Symptom Inventory; SLAM = Systemic Lupus Activity Measure; SDI = Systemic Lupus International Collaborative Clinics Damage Index; SF-36 = The Medical Outcome Study Short Form-36; MoCA = Montreal Cognitive Assessment.

TABLE I. CONTINUATION

	Study Design (data collection)	Neuropsychiatric syndrome	Screening Measure	Diagnostic/ Verification Measure(s)	No. of SLE patients	Control patients	Frequency of affected	Results	
								Psychometric properties	Relevant points
Iverson et al[22] (2002)	Survey study (prospective)	Depression	BDI-II BCMDI	–	103 (self-report)	H = 136	–	–	15% patients classified as probably depressed by BDI-II scored in the normal range on the BCMDI
Julian et al[40] (2011)	Cross-sectional study (prospective)	Mood disorders	CES-D	MINI	150	–	Mood disorder=26%	Sn = 87% Sp = 87%	92% correctly classified patients with MDD
Hyphantis et al[44] (2011)	Cross-sectional study (prospective)	Depression	PHQ-9 Greek version	MINI	62*	–	MDD = 25,4%#	Sn = 81,2%# Sp = 86,8%#	
Mosca et al[45] (2011)	Case-control study (prospective)	Neuropsychiatric syndromes	Pilot questionnaire	Physician evaluation	139§ (NPSLE=58)	Non-NPSLE =81	–	Sn = 93% Sp = 25%	Association of non-specific symptoms may result in higher score than severe manifestations by themselves

*62 SLE patients out of a 558 rheumatologic diverse sample; # These results were calculated from the whole (558 patient) sample; § The sample was formed by 139 SLE patients, 58 with active or inactive NPSLE (case group) and 81 with SLE without history of neuropsychiatric lupus (control group).
SLE= Systemic Lupus Erythematosus; H = Healthy; CD = Cognitive dysfunction; NPSLE= Neuropsychiatric Lupus; NRS = Scripps Neurologic Rating Scale; Sn = Sensitivity; Sp= Specificity; PPV= Positive predictive value; NPV= Negative predictive value; Formal NP testing = neuropsychological test battery derived from the ACR recommendations 1; PDQ = Perceived Deficits Questionnaire; BDI-II = Beck Depression Inventory – Second Edition; BCMDI = British Columbia Major Depresion Inventory; CES-D = Center for Epidemiologic Studies Depression Scale; MINI = Mini-International Neuropsychiatric Interview; PHQ-9= Patient Health Questionnaire-9; MDD= Major Depressive Disorder.

computerized battery of neuropsychological tests, developed by U.S. military in order to assess the cognitive repercussions of chemical agents, extreme environments and fatigue on cognitive processing speed and efficiency[27].

Holliday *et al*, in 2003, was the first to suggest the use of ANAM as a screening tool in the SLE context. This study administered both ANAM and a traditional test battery based on ACR Ad Hoc Committee on NPSLE recommendations in a sample of 67 ethnically mixed SLE patients enrolled in a large prospective cohort[27].

The results showed that many ANAM measures correlated with the scores from the traditional neuropsychological tests. It was also found that age is of little relevance on the variance observed when accounted alone but it acts as a powerful moderator variable when is entered with ANAM variables into a linear regression model. This model accounted for about 61% of the variance in the average T-score on the traditional tests[27].

A Roebuck-Spencer, a 2006 publication, confirms the positive correlation between ANAM and traditional neuropsychological testing. In this study the performances in the two batteries are compared in a sample of 60 SLE patients participating in a large SLE cohort on biomarkers of cognitive dysfunction. ANAM test battery demonstrated a sensibility of 76,2% and specificity of 82,8% on the classification of individuals with probable cognitive impairment versus no impairment in neuropsychological testing. ANAM remained a good screening tool when depression and sleepiness were present, measured with validated self-reported measures of sleepiness and depressed mood, suggesting that it is not confounded by these. Furthermore, significant correlation between ANAM's mood scale and BDI-II was found, supporting its use as a potential mea-

sure of emotional distress in SLE patients[36].

A 2010 study by Hanly *et al*, sought out to compare ANAM battery tests' performance in a sample of 29 healthy controls, 68 Lupus (SLE), 33 Rheumatoid Arthritis (RA) and 20 Multiple Sclerosis (MS) patients[31].

The results showed a cognitive impairment of 11--50% in SLE patients (depending on stringency of classification rules) when compared with locally recruited healthy controls. However this frequency was comparable with the 9-61% calculated frequency in RA patients and lower than that calculated for MS patients, 20-75%. The frequency difference between SLE patients and patients with stable MS disease is expected but the observed comparability of frequencies between SLE patients and patients with a disease that does not affect primarily the CNS, as RA, raised questions about the presumed etiology of deficits detected by ANAM. The authors suggested that the measures evaluated by the ANAM battery do not distinguish between impaired mental processing and speed sensoriomotor deficiencies and can instead represent CNS immunosuppressive toxicity. These findings lead to the conclusion that ANAM cannot be used to assess dysfunction on specific cognitive domains and it was not designed as a substitute for formal neuropsychological assessment[31].

In 2007 Brunner et al studied the statistical properties of the pediatric ANAM (ped-ANAM) in a childhood-onset SLE sample. Ped-ANAM and a battery of formal neuropsychological tests (based on published data for SLE adults) were performed in a sample of 27 children with a median age of 16,5 years recruited from a pediatric rheumatology clinic. A trend towards worse performance of participants with CD compared to those without was observed in every performance parameter of the battery but statistically significant differences between the two groups were only reached for 3 out of the 10 ped-ANAM scores. Furthermore, statistical significant correlations were found between Ped-ANAM scores and formal neuropsychological tests. Ped-ANAM was found as a promising tool to screen cognitive dysfunction in SLE children presenting validity and promising sensitivity and specificity[15].

The Cognitive Symptom Inventory (CSI) is a self--administered paper questionnaire consisting of 21 items focused in evaluating the subject's ability to perform several cognitive functions and activities of daily life.

In 2002, Alarcón *et al* published a study which aimed to determine the factor structure of the CSI and the production of 4 factor scales and their correlation with 3 self-report measures of cognitive dysfunction and self-report measures of fatigue, helplessness, self--efficacy, pain, social support and use of maladaptative coping skills. The sample, drawn from a large prospective cohort (LUMINA), consisted of 156 ethnically mixed SLE patients[17].

The four main factors assessed by the CSI were found to be: Attention/Concentration, Pattern/Activity Management, Intermediate Memory and Initiation of Executive Functions. Despite the small shared amount of common variance between these four factors, the correlation was not high enough that they duplicate one another[17].

Modest statistically significant correlations were also found between CSI cognitive factor scales and SLAM measure of Cortical Dysfunction, SF-36 measure of Mental Functioning, SDI measure of Cognitive Impairment, measures of fatigue, psychological distress, social support, maladpative coping skills, self-efficacy and pain[17].

CSI patients' responses were found not to be confounded by social-demographic or clinical variables. The questionnaire was completed in an average time of 10 minutes and with minimal paraprofessional help regardless of ethnical backgrounds or administered language[17].

The Montreal Cognitive Assessment (MoCA) is a validated, one-page, physician-administred questionnaire used on the identification of mild cognitive dysfunction in the elderly[32].

Published in 2011 by Adhikari *et al* there is a study that aims to evaluate MoCA as a screening tool for detection of cognitive dysfunction in SLE patients. In a sample of 44 SLE patients and age, sex and race-matched RA patients were applied both the MoCA and, as gold standard, the ANAM[35]. Results demonstrate that to a standard cutoff score of 26 the sensitivity of MoCA was 83%. The specificity was 73% with a positive predictive valued of 50% and a negative predictive value of 92%. These results suggest that MoCA has the potential to be used as a screening tool for the detection of SLE with probable cognitive dysfunction[32].

In 2008, Kozora *et al* publishes a study aimed to examine the screening utility of the standardized neurologic evaluations in the identification of SLE patients with probable cognitive dysfunction. All the participants in the study were already enrolled in a large pros-

pective cohort of cognitive functioning and neuro-imaging. The participants were selected based on the examination of their clinical history and on physician interview in order to identify the ones with history of neuropsychiatric diseases or depression. The Scripps Neurologic Rating Scale (SNRS) and the short ACR-SLE battery were administrated to all the participants (SLE=67, Controls=29)[37]. The SNRS is a 22 item neurologic exam developed for the clinical evaluation of patients with multiple sclerosis. The prevalence of cognitive dysfunction in the sample was 20,9%. The non-NPSLE group had worse outcomes on SNRS global score than the control group (p<0,001). However after analysis of the SNRS parameters, the one responsible for the statistically significant difference was "mentation and mood". Nevertheless two patients were excluded after the initial screening process during the administration of the neurologic examination by the neurologist suggesting that the SNRS can assure that overt neurologic dysfunction is not present and assist in identifying non-NPSLE patients[37].

Julian *et al* publishes, in 2011, a study aimed at the evaluation of the utility of telephone screening and self-report assessments of cognitive complaints in detecting cognitive impairment in individuals with SLE and RA[28]. Two screening measures were evaluated: a 12-15 minutes telephone interview based on three neuropsychological tests (see article for details) and the Perceived Deficits Questionnaire (PDQ), a five-question, self-administered questionnaire. A validated neuropsychological battery based on the short ACR-SLE battery was used as "gold standard".

The sample of 138 SLE patients and 84 RA patients was drawn from two large cohorts of SLE and RA patients, respectively. The cognitive dysfunction rate was 27% in the SLE group. The telephone screening had 77% sensitivity, 65% specificity, 94% negative predictive value, 43% positive predictive value and 67% of the patients were correctly classified as cognitively impaired, in the SLE group. While the PDQ had 64% sensitivity, 65% specificity, 83% negative predictive value, 38% positive predictive value and 64% of the patients were correctly classified as cognitively impaired, in the SLE group. Contrary to the telephone screening measure, the PDQ was not a significant predictor of cognitive impairment when adjusted for social-demographic data and depression[28].

MOOD AND ANXIETY DISORDERS
The reported prevalence of mood and anxiety disorders

in recent studies ranges between 12,4-60%[5,14,28,38-41] and 6,4-46,5%[5,29,39,41], respectively.

The ACR Ad Hoc Committee on NPSLE recommends the use of standardized instruments like the Center for Epidemiological Studies - Depression Scale (CES-D) and the Hospital Anxiety and Depression Scale (HADS) for the diagnosis of mood and anxiety disorders[1].

Several associations have been sought out by different studies in order to understand the pathophysiology of these disorders.

The association between short disease duration and anxiety disorders was described in a 2011 study by Hawro *et al*, raising the hypothesis that anxiety was a consequence of the inadequate information about the disease suggesting that at least part of the anxious disorders encountered in NPSLE have an adaptive background[33].

Kozora *et al* in 2007 compared the performances of depressed SLE patients (n=13), depressive non-SLE patients (n=10) and healthy controls (n=25) in the short ACR-SLE battery and a comprehensive neuropsychological battery. The results of this study not only confirmed the association between depression and cognitive dysfunction[42] but also validated the short ACR-SLE battery for the diagnosis of cognitive dysfunction in depressed SLE patients[43].

In a survey study published by Iverson *et al* in 2002, two screening depression measures were compared, Beck Depression Inventory-Second Edition (BDI-II) and the British Columbia Major Depression Inventory (BCMDI), both instruments constructed according to the diagnostic criteria of DSM-IV for depression. The sample consisted of 103 self-reported lupus patients (no attempt was made to confirm the diagnosis) and 136 healthy controls. The self-reported SLE group had higher rates of depression and vegetative symptoms (fatigue, difficulty falling asleep, sadness, etc.) than the control group. The results suggest a overestimate of depression diagnosis by BDI-II, a valid and reliable screening measure of depression. Fifteen percent of the patients identified as depressed on the BDI-II scored in the normal range on the BCMDI, and 46% scored in the possibly depressed range. Therefore, it is possible that the BDI-II over-identified depression in this sample[22].

In a 2011 study by Julian *et al*, the Center for Epidemiological Studies - Depression Scale (CES-D) is compared with the Mini-International Neuropsychiatric Interview (MINI), a validated diagnostic method based on structured clinical interview, in a sample of

150 SLE patients drawn from a prospective cohort of 957 lupus patients. In this sample 26% of the patients were diagnosed with a mood disorder and 17% with major depressive disorder measured by the MINI. The results showed a 92% of corrected classified patients with major depressive disorder and a 87% sensibility and specificity in detection of any mood disorder with the CES-D40.

Hyphantis *et al*, in 2011, studies the psychometric characteristics of the greek version of the Patient Health Questionnaire-9 (PHQ-9) in a diverse rheumatologic sample of 558 patients (62 lupus patients). The PHQ-9 is a, 9 question, self-administered, simple, questionnaire used on the screening and severity assessment of depression. The results showed 25,4% prevalence of Major Depressive Disorder (MDD), measured by MINI, and a 81,2% and 86,8%, sensitivity and specificity, respectively, of identifying MDD, in the greek version PHQ-9[44].

PILOT SCREENING TOOL

Mosca *et al* published, in 2011, a study aimed to create a questionnaire, to be administered by physicians, that could be used as a screening tool for the identification of neuropsychiatric manifestations in SLE patients with no obvious CNS involvement, for further evaluation[45].

Starting from group of 112 questions drawn from 41 questionnaires aimed at assessing neuropsychiatric manifestations similar to those prevalent in NPSLE, a panel of experts and statistic analysis created a draft questionnaire with 62 items. This draft questionnaire was then tested in 139 SLE patients from 11 european centers and the results were compared with clinical diagnosis made by a specialist. After additional statistical analysis, the final questionnaire consisted of 27 items, 12 referring to the central nervous system symptoms and 15 to psychiatric ones.

For a cutoff value of 17 the questionnaire had a sensitivity and specificity of 93% and 25% respectively. It was found that the association of non-specific symptoms (e.g. subjective complain of cognitive dysfunction or headache) may determine a higher score than serious manifestations such as seizures alone. All the initial included items aimed at the assessment of peripheral nervous system symptoms were excluded based on the methodology used. Despite the intent to be administered by a physician the authors considered the questionnaire to be simple enough to be filled by the patient himself[45].

DISCUSSION

One of the most controversial topics in the study of the psychiatric manifestations in the lupus context is their etiology. In fact, despite the high prevalences reported across studies, it remains undisclosed if the psychiatric manifestations in SLE are a direct consequence of the autoimmune disease or secondary to it. Several factors can explain the secondary nature of these disorders like the stress of having a chronic disease, the lack of social support or the use of immunosuppresive therapy[39].

Psychiatric syndromes are rarely diagnosed early in their course due to their initially faint clinical manifestations and lack of accepted, valid and accessible methods of detection which leads to underdiagnosis and undertreatment of these conditions. Thus, a simple, sensitive screening test would serve to improve quality of management of lupus patients[32]. On the other hand, randomized clinical trials are necessary in SLE to fully understand the benefit-harm tradeoffs of screening these psychiatric manifestations[40].

This review clearly shows that a lot more research needs to be done in order to validate the screening tools suggested across the literature. With the exception of ANAM, all the instruments proposed across the literature were studied only once.

The ANAM presents as the most analyzed of the screening tools, presenting good sensitivity and specificity (76.2% and 82.4%, respectively) on the distinction of SLE patients with cognitive dysfunction in formal neuropsychological testing from those without. ANAM, compared with formal neuropsychological testing, appears to be less confounded by variables such as, education, English proficiency and ethnic differences[27]. Its accessibility, self-administration, low practice-effects, reduced cost and validity in depressed lupus patients[27,36] makes of ANAM a promising screening tool. The finding that it may be confounded by immunosuppressive toxicity and/or sensoriomotor deficits[31] may not be as relevant clinically as it is etiologically since regardless of cause attribution, cognitive dysfunction is a co-morbidity that needs to be addressed when diagnosed.

Preliminary results determined that Cognitive Symptom Inventory (CSI), a 10 minute self-administered paper test, has the potential to be used as a screening instrument on the identification of SLE patients with probable cognitive dysfunction. Revision of some of the items' contents, expansion of the questionnaire

so it covers other cognitive domains, study of its psychometric characteristics and testing it in different samples are some of the issues that need to be addressed in further studies in order to validate the CSI as a screening tool[17]. Contrary to CSI, the Perceived Deficits Questionnaire, a 5 question self-administered questionnaire was found to be a weak predictor of cognitive impairment since it was confounded by social-demographic data and depression[28].

The Montreal Cognitive Assessment (MoCA), a physician administered questionnaire, presented a 83% sensitivity and 73% specificity. However the "gold standard" used was not formal neuropsychological testing but the ANAM, presenting a vulnerability of the study[32].

In the Kozora et al study on the utility as a screening tool of the Scripps Neurologic Rating Scale16 the results were not too impressive since despite the significant difference between SLE and control groups in identifying cognitive dysfunction, "mentation and mood" was the parameter responsible for the statistically significant difference. Furthermore, one aspect that was not referred in the study was how long did it take to administer the neurologic exam, essential to determine the true time-cost efficiency of it.

Another promising screening instrument is the Telephone Screening studied by Julian *et al*, the 43% positive predictive value and 93% negative predictive value presented by this tool, is an advantage in that permits to exclude with greater confidence individuals without cognitive impairment[28].

It is somehow surprising that despite the high frequencies reported of mood and anxiety disorders among lupus patients, and the number of measures available aiming the screening of these disorders, only two studies were found comparing the performances of screening tests in the lupus context. In fact, only in 2011 the Center for Epidemiological Studies Depression Scale, recommended in 1999 by the ACR Ad Hoc Committee on NPSLE, as a screening tool to identify patients with probable mood disorders, was tested, presenting the Julian et al study a 87% sensitivity and specificity in detecting mood disorders[40].

Some of the screening tools presented are not available to non-english speakers due to lack of validated translations. The ANAM, the most studied cognitive dysfunction screening tool, is an example of that. This constitutes an obvious limitation not only in the clinical but also in the research context. Instruments like, CES-D, MoCA, PHQ and BDI-II however, have been translated and validated in multiple languages and are thus available to be tested in different settings. The 2011 study published by Hyphantis *et al* that validated the greek version of the PHQ-9 in a large and diverse rheumatologic sample[44], is an example of the type of study that needs to be done in order to increase the usage of screening tools in clinical practice.

Pediatric Neuropsychiatric Lupus is even less understood than the adult variant due to lack of research targeting this specific age group. The definition cases and diagnostic criteria recommended by the ACR Ad Hoc Committee on NPSLE are being inadequately used in children. Williams et al demonstrated that depending on the methodology used to classify cognitive impairment in children, its prevalence ranged from 7,3% to 63,4% in the same sample. More than that, no significant differences were encountered in tested domain scores as well as cognitive dysfunction prevalence estimates between lupus children and healthy controls[19]. Another difficulty in studying pediatric lupus is the small sample available, one of the main limitations of the Brunner et al study[15] that examined the usefulness of the pediatric version of ANAM in a small sample of 27 lupus children.

Mosca et al approached screening testing in a holistic way, creating a physician-administered simple questionnaire to screen neuropsychiatric events. The main limitation of the study is the lack of items that assess the peripheral nervous system, justified by the authors as a result of the low prevalence of these phenomena in the lupus context. Despite the low specificity demonstrated (25%) this is a revolutionary study that demonstrated promising preliminary results[45].

There is still a long way to go regarding the study of psychiatric manifestations in the lupus context. Sample selection, classification of impairment and attribution of cause are parameters that need to be defined and standardized in order to compare studies and draw conclusions. Most of the screening tools studied in this context present promising, yet preliminary results. These tools need to be further studied in other samples and study designs in order to validate their usage in clinical practice. The translation into multiple languages will not only allow the possibility of screening non--english patients but also stimulate further research.

On the other hand, regardless of the high frequency of these psychiatric manifestations, clinical trials on their treatment are scarce in the literature, leaving us wondering if there is a true benefit into early detection of these manifestations.

CORRESPONDENCE TO

Joana Vicente Vargas
Rua Engº Rui Cruz, B22
8000 Faro, Portugal
E-mail: joanavvargas@gmail.com

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