RHEUMATOLOGY

Rheumatology 2015;54:891–898
doi:10.1093/rheumatology/keu384
Advance Access publication 21 October 2014

Original article

Development and validation of a new algorithm for attribution of neuropsychiatric events in systemic lupus erythematosus

Alessandra Bortoluzzi[1], Carlo Alberto Scirè[2], Stefano Bombardieri[3], Luisa Caniatti[4], Fabrizio Conti[5], Salvatore De Vita[6], Andrea Doria[7], Gianfranco Ferraccioli[8], Elisa Gremese[8], Elisa Mansutti[6], Alessandro Mathieu[9], Marta Mosca[3], Melissa Padovan[1], Matteo Piga[9], Angela Tincani[10], Maria Rosaria Tola[4], Paola Tomietto[11], Guido Valesini[5], Margherita Zen[7] and Marcello Govoni[1], on behalf of the Study Group on Neuropsychiatric Systemic Lupus Erythematosus of the Italian Society of Rheumatology

Abstract

Objective. The aim of this study was to develop and validate an algorithm to assist the attribution of neuropsychiatric (NP) events to underlying disease in SLE patients.

Methods. Phase 1 identified and categorized candidate items to be included in the algorithm for the attribution of an NP event to SLE and their relative weights through a literature-informed consensus-driven process. Using a retrospective training cohort of SLE, phase 2 validated items selected in phase 1 and refined weights through a data-driven process, fitting items as independent variables and expert evaluation (clinical judgement) as reference standard in logistic models. Phase 3 consisted of a validation process using an external multicentre retrospective SLE cohort.

Results. Phase 1 identified four different items: timing of the NP event, type of event, confounding factors and favouring factors. The training and validating cohorts included 228 and 221 patients, respectively. Each patient experienced at least one NP event characterized using the ACR case definition. In these samples, items selected in phase 1 showed good performance in discriminating patients with NPSLE: the area under the receiver operating characteristic curve using dichotomous outcomes was 0.87 in the training set and 0.82 in the validating set. Relevant cut-offs of the validated score identify events with a positive predictive value of 100% (95% CI 93.2, 100) and 86.3% (95% CI 76.2, 93.2) in the training and validating cohorts, respectively.

Conclusion. A new algorithm based on a probability score was developed and validated to determine the relationship between NP events and SLE.

Key words: systemic lupus erythematosus, neuropsychiatric, attribution model.

[1]Department of Medical Science, Section of Hematology and Rheumatology, University of Ferrara and Azienda Ospedaliero Universitaria Sant'Anna di Cona, Ferrara, [2]Epidemiology Unit, Italian Society of Rheumatology, Milan, [3]Rheumatology Unit, Department of Clinical and Experimental Medicine, University of Pisa, Pisa, [4]Department of Neuroscience, S. Anna Hospital, Cona, Ferrara, [5]Department of Internal Medicine and Medical Specialties, Sapienza University of Rome, Rome, [6]Rheumatology Clinic, Azienda Ospedaliero Universitaria 'S. Maria della Misericordia' and DSMB, Department of Medical and Biological Sciences, University of Udine, Udine, [7]Department of Clinical and Experimental Medicine, Division of Rheumatology, University of Padova, Padova, [8]Division of Rheumatology and Internal Medicine, Institute of Rheumatology and Affine Sciences, CIC, Catholic University of the Sacred Heart, Rome, [9]Rheumatology Unit, Department of Medical Sciences, University of Cagliari and AOU University Clinic, Cagliari, [10]Rheumatology and Clinical Immunology Unit, Spedali Civili and University of Brescia, Brescia and [11]Internal Medicine, AOU 'Ospedali Riuniti' of Trieste, Trieste, Italy

Submitted 22 May 2014; revised version accepted 1 August 2014

Correspondence to: Alessandra Bortoluzzi, Department of Medical Science, Section of Hematology and Rheumatology, University of Ferrara, Via Aldo Moro, 844124 Cona, Italy. E-mail: brtlsn1@unife.it

CLINICAL SCIENCE

Introduction

Neuropsychiatric (NP) involvement in SLE consists of a heterogeneous variety of neurological and psychiatric syndromes, none of which are specific for SLE and the aetiopathogenesis of which are still not completely known. Therefore their relationship to the underlying disease (i.e., attribution) is difficult to assess.

In 1999 the ACR Research Committee developed a standard nomenclature and a set of case definitions for NPSLE. This significant advance provided a uniform methodology to recognize patients with NPSLE [1], but the final decision about the attribution of an occurring NP event, whenever satisfying the ACR case definition, still remains a clinical challenge, mainly based on expert opinion.

Some studies have already looked at this issue, suggesting attribution models yielding appreciable results with a proportion of NP events attributed to SLE ranging from 16.8 to 30.5 [2–7]. This study aims to develop and validate a new algorithm, which could be translated into a simple probability score, to determine the strength of the relationship (i.e., attribution) between a given occurring NP event and the underlying SLE.

Patients and methods

On behalf of the Italian Society of Rheumatology, a research project started in 2009. A panel of experts was established, including 18 rheumatologists, 1 neurologist, 1 neuroradiologist and 1 psychiatrist—all members of the Italian Study Group on Neuropsychiatric SLE, instituted in 2003. The project was divided into three phases.

Phase 1: item selection, categorization and weighting

Phase 1 was a literature-informed consensus-driven process aimed at identifying, categorizing and weighting candidate items that could be relevant with respect to the attribution process and to be included in the algorithm.

Item selection and categorization

Literature was systematically searched via PubMed until June 2011, using a combination of MeSH and free-text keywords (see the search strategy reported in the supplementary material, available at *Rheumatology* Online). The expert panel then identified a list of candidate items to be evaluated. According to the Delphi method [8, 9], a first round of consultations was made by sending electronic questionnaires and the experts were asked to select a restricted number of items to be listed in the algorithm. A degree of consensus, measured on a 10-point Likert scale, of >70% was judged to be adequate. A second round was performed by resending an electronic version of the same questionnaire incorporating the results obtained in the previous version. Due to the complexity of the task, unresolved issues were expected. To resolve these issues, after the second electronic round, a structured meeting was organized at the XLVIII Congress of the Italian Society of Rheumatology, held in November 2011. After this face-to-face consultation, consensus was reached on the final definition of those items to be included in the algorithm. In a third round of consultation, each selected item was categorized into subheadings to allow their subsequent weighting.

Item weighting

Another questionnaire was submitted to the expert panel to assign a positive or negative value to each subheading of the selected item so as to indicate the strength (high) or weakness (low) of their relationship with the underlying disease. A numerical score (weight) ranging from 0 to 1 was defined, where 0 was deemed as irrelevant or not applicable, 0.5 as relevant and 1 as most relevant. To simplify the calculation, the single-item scores (positive or negative) were then rescaled. The sum of the partial scores from each of the four items yielded a total score ranging from 0 to 10, assuming that the higher the score, the greater the probability a given NP event is related to SLE.

Phase 2

Phase 2, a data-driven process, validated the selected items and refined weights based on the data of a training retrospective cohort of SLE.

Cohorts and patient selection

A first training cohort was recruited between 1 January 2000 and 31 December 2007 at the Rheumatology Unit of the S. Anna Ferrara University Hospital, a tertiary referral centre for SLE. All consecutive patients fulfilling the 1997 revised ACR criteria for SLE were retrospectively analysed [10].

Phase 3

A second external multicentre validating cohort was recruited from seven rheumatology centres in different geographical areas of Italy and invited to participate in the study. The centres provided data from patients with SLE and NP manifestations observed from 1 January 2007 to 31 December 2011. All patients satisfied the revised ACR criteria for SLE [4]. Each selected patient in training and validating cohorts had experienced one or more NP events characterized using the ACR case definition. Secondary causes, other than SLE, known to induce NP manifestations deemed as exclusion criteria by the 1999 ACR glossary were ruled out after extensive evaluation. Only ascertained cases with a follow-up of at least 1 year were included in this study. The study was approved by the local ethics committee (Comitato Etico della Provincia di Ferrara) and written consent has been obtained from all enrolled subjects in accordance with the Declaration of Helsinki.

Collected variables

Clinical, demographic and serological data were assessed by retrieving information from clinical records. Laboratory data collected are listed in Table 1.

Disease activity was routinely assessed by the SLEDAI [11] at each visit and also measured at the time of onset of the NP manifestation without taking into account the NP items [12]. A SLEDAI score >6 was assumed to be indicative of active disease. Damage was calculated by the SLICC/ACR Damage Index [13].

Table 1 List of demographic and sero-immunological variables and instrumental examinations evaluated

Age at the time of first NP event, years
Sex (female/male)
Disease duration at the time of first NP event, years
ANA (by indirect immunofluorescence method with Hep-2 as substrate)
Anti-DNA antibodies (by enzyme immunoassay and confirmed by indirect immunofluorescence with *Crithidia luciliae* as substrate)
Antibodies to extractable nuclear antigen (by ELISA) aPL by standardized ELISA kit
Lupus anticoagulant (by kaolin clotting time and Russell viper venom test, according to the recommendation of the Scientific and Standardization Committee of the International Society of Thrombosis and Hemostasis)
Anti-ribosomal P antibodies (tested by the commercial ELISA kit or according to the local standard) C3 and C4 (g/l) detected by nephelometry
CSF examination (data were taken into account, when indicated, only for diagnostic purposes and for the final assessment of the neurological pictures)
Electroencephalography
Brain MRI
SPECT
Multimodality evoked potentials
Electromyography
Carotid duplex US
Doppler ECG

Case definition

All NP events occurring within the defined timeframe were identified according to the diagnostic workup indicated for the various NP syndromes as advised by the formal case definition nomenclature of the 1999 ACR classification criteria, after exclusion of secondary causes. When prompted by the clinical context, patients underwent appropriate instrumental examinations (Table 1). When suggested by the clinical picture, neuropsychological assessment was performed to investigate cognitive deficits using the recommended formal battery of tests [1, 14–16].

Cognitive impairment was considered to be mild if the assessments yielded altered results in fewer than three domains and clinically relevant when three or more domains were involved [2].

NP events were categorized as single or multiple, central or peripheral and focal or diffuse according to Bertsias *et al*. [17]. Recurrence of the same type of event was also recorded, by counting every observed event. For all of the retrieved NP events the clinical judgement about their attribution or not to the underlying SLE, formulated at the time of their occurrence by the local multidisciplinary attending team, was recorded. The clinical judgement about the relationship between each NP event and SLE was categorized as follows: related, uncertain or not related. In phase 3 the algorithm was externally validated using a different multicentre retrospective validating cohort.

Data analysis

Using the clinical judgment as outcome, the items selected in phase 1 were tested using ordinal logistic models after evaluation of proportionality of odds assumption. The coefficients of each level of the different categories of the included items were internally validated using a bootstrap procedure (1000 samples).

After normalization—varying between 0 and 10—empirical coefficients were used to refine those defined a priori, giving more weight to a priori than to empirical coefficients. Final coefficients were rounded to multiples of 0.5. The sum of these coefficients was used to calculate an individual score reflecting the increasing probability of NPSLE.

The performance of the classification of this score was tested against the reference standard (i.e. clinical judgement) and was evaluated by ordinal logistic models and by calculating the Harrell *c*-statistics in both the training and validating cohorts. Separate logistic models using binary outcomes (related *vs* not related/uncertain and related/uncertain *vs* not related) were also fitted. Based on the receiver operating characteristic (ROC) tables using binary outcomes, cut-offs associated with misclassification $<10\%$ were chosen to identify categories of attribution of the NP event to SLE: related, uncertain or not related. Sensitivity, specificity, positive predictive value (PPV) and negative predictive value (NPV) were calculated for each cut-off. All the analyses were performed using Stata 11 (StataCorp, College Station, TX, USA).

Results

Phase 1: item identification, categorization and weighting

Item selection

From 2720 references, 47 papers were examined by the expert panel. After an in-depth analysis, seven were found to deal directly with the research questions [2–4, 12–20]. After the first and second round of the Delphi survey, three candidate items were identified as relevant and were included in the algorithm: (i) the time onset of the NP event, (ii) the presence of concurrent or confounding non-SLE factors (i.e. associations as suggested by the 1999 ACR glossary) and (iii) the type of NP event (major

vs minor or common according to what has been proposed by Ainiala *et al*. [3] (Table 2). A fourth item, called favouring factors (i.e. supporting attribution), not covered by the 1999 ACR classification, was added and included both the specific SLE-related risk factors reported in the European League Against Rheumatism (EULAR) recommendations (17) and further information considered relevant for the attribution process by the expert panel.

Item categorization

In the third round, the first item (time onset of NP event) was categorized in three subheadings, taking into account the time of appearance of the NP picture with respect to the time onset of SLE: before (>6 months), concomitant (within 6 months) or after; the second item (typology of the NP picture) was categorized in two subheadings, depending on the presence or absence of those NP pictures deemed as minor or common. The third (confounding factors) and fourth (favouring factors) items, related to each NP event, were categorized in the following subheadings: absent, at least one and more than one (Table 2). Two detailed checklists for the third and fourth items were then established and are reported in detail in supplementary Tables S1 and S2, respectively, available at *Rheumatology* Online.

Item weighting

In the third round, a priori weight (partial score) resulting from the consensus process was assigned to each subheading of the four items incorporated in the algorithm (Table 2).

Phase 2: data-driven process

In the training retrospective cohort, 228 patients with an established diagnosis of SLE with at least one NP event in their history were judged eligible for the study, mainly women (212 female and 16 male), with median age at first NP event 42.8 years (S.D. 14.7). The number of NP events recorded in this cohort was 419, with single events in 108 patients and multiple (range 2–6) events in the remaining 120 patients. Headache was the most frequently observed manifestation (27.7%), followed by cerebrovascular disease (CVD), (16.2%) and mood disorder (16%). A total of 128 NP events were focal (30.5%) and 291 were diffuse (69.5%); 32 NP manifestations (7.7%) involved the peripheral nervous system (PNS) and 92.3% (387 events) involved the CNS (Table 3).

An additional 221 patients, again with at least one NP event in their history, were enrolled in the external validation cohort [193 female and 28 male, median age at first NP event 32.8 years (S.D. 10.8)], for a total of 428 events distributed as indicated in Table 3. A single NP event was recorded in 117 patients and multiple events (up to a maximum of eight) were recorded in the remaining cases. Also, in the validating cohort, headache was the most frequently reported event (22.2%), followed by CVD (14.3%) and seizures (14.3%).

Mean disease duration at the time of first NP event was 5.9 years (S.D. 4.7) in the training cohort and 7.4 years (S.D. 6.3) in the validating cohort. In the external cohort, organ involvement was more common (i.e. arthritis, nephropathy and cutaneous involvement being the most represented). Background treatment was similar in the two cohorts for oral glucocorticoids, antimalarials and immunosuppressive drugs.

Empirical coefficients derived from the multivariate ordinal logistic analysis are presented in Table 4. Bootstrap validation confirmed the internal validity of the estimated coefficients. However, given the high variability of the

Table 2 Categorization and weighting of the selected items incorporated into the algorithm

	Score
Item 1. Time of the onset of NP event with respect to SLE clinical onset	
Before (>6 months before SLE onset)	0
Concomitant (within 6 months of SLE onset)	3
After (>6 months after SLE onset)	2
Item 2. Minor or not specific NP events as defined by Ainiala *et al*. [2]	
Present (i.e. minor or common NP events as proposed by Ainiala *et al*. [2])[a]	0
Absent (i.e. NP events other than those proposed by Ainiala *et al.* [2])[a]	3
Item 3[b]. Confounding factors or not SLE-related associations as defined by the ACR glossary [1]	
None or not applicable	2
Present (one confounding factor)	1
Present (more than one confounding factor)	0
Item 4[b]. Additional (or favouring) factors	
None or not applicable	0
Present (one additional or favouring factor)	1
Present (more than one additional or favouring factor)	2

[a]List of NP pictures deemed as minor or common known to occur frequently in normal healthy population controls: headaches, anxiety, mild depression (mood disorders failing to meet the criteria for major depressive-like episodes), mild cognitive impairment (deficit in fewer than three of the eight specified cognitive domains) and polyneuropathy without electrophysiological confirmation. [b]A list of confounding and favouring factors is given in supplementary Tables S1 and S2, respectively, available at *Rheumatology* Online. NP: neuropsychiatric.

TABLE 3 NP manifestations recorded in training and validating cohorts

Type of event	Training cohort ($n = 228$)		Validating cohort ($n = 221$)	
	n	%	*n*	%
CNS involvement				
Headache	116	27.7	95	22.2
CVD	68	16.2	61	14.3
Mood disorder	67	16.0	49	11.5
Cognitive dysfunction	61	14.6	56	13.1
Seizures	19	4.5	61	14.3
Anxiety	15	3.6	28	6.6
Psychosis	13	3.1	17	4
Movement disorder	7	1.7	3	0.7
Acute confusional state	7	1.7	13	3
Aseptic meningitis	3	0.7	0	0
MS-like syndrome	3	0.7	4	0.9
Myelopathy	1	0.2	4	0.9
PNS involvement				
Polyneuropathy	17	4.0	16	3.7
Cranial neuropathy	14	3.4	9	2
Mononeuropathy	6	1.4	8	1.9
Myasthenia gravis	2	0.4	2	0.5
Autonomic neuropathy	0	0	1	0.2
Plexopathy	0	0	0	0
Guillain–Barre syndrome	0	0	1	0.2
Events (total)	419		428	

CVD: cerebrovascular disease; MS: multiple sclerosis; NP: neuropsychiatric; PNS: peripheral nervous system.

estimates, updating was carried out giving more weight to the a priori coefficients (3:1).

Phase 3: external validation

The performance of the algorithm based on the updated coefficient was good in the training set using ordinal logistic models (Harrel's *c*-statistics 0.853) and validating set (0.779). The area under the curve (AUC) of the ROC curve using dichotomous outcomes (related *vs* uncertain/not related) showed the following values: 0.866 in the training set and 0.816 in the validating set (Fig. 1). The AUC of the ROC curve for NP events clustered into CNS *vs* PNS and diffuse *vs* focal NP disease in the validating set was 0.790 for focal ($n = 86$ patients) and 0.784 for diffuse ($n = 124$ patients) events and 0.812 for CNS ($n = 195$ patients) and 0.852 for PNS ($n = 15$ patients) manifestations.

Based on the ROC table for a dataset combining training and validating cohorts, the best single cut-off was $\geqslant 6$, with sensitivity 83% (95% CI 77.7, 87.5), specificity 70.9% (95% CI 63.9, 77.3), a PPV of 78.8% (95% CI 73.4, 83.6) and an NPV of 76.1% (95% CI 69.1, 82.2) (Fig. 2). Given the intrinsic uncertainty of the diagnosis even in the reference standard, two additional cut-offs for misclassification to $<10\%$ were also calculated. Consistently an event with a score higher than 7 showed an estimated probability of being SLE-related (PPV) of 100% (95% CI 93.2, 100) and 86.3% (95% CI 76.2, 93.2) in the training and validating cohorts, respectively, while an event with a score lower than 3 showed a probability of being SLE-unrelated (NPV) of 93.8% (95% CI 69.8, 99.8) and 85.7% (95% CI 63.7, 97) in the training and validating cohorts, respectively. Overall, by using these cut-offs, the percentages of NP events deemed as SLE related were 32.7% and 33.8% in the training and validating cohorts, respectively.

Discussion

NP involvement in SLE is a well-recognized complication heavily influencing morbidity and mortality. So far the attribution of NP events, i.e. the demonstration of a strict cause–effect relationship linking an NP event with the underlying disease, remains a critical issue. In 1999 the ACR Research Committee provided an important tool for research and clinicians, enabling a better case definition, mainly based on a rigorous exclusion process [1]. Nonetheless, in studies conducted after the publication of these criteria, the reported prevalence of NP manifestations in different series still ranged between 37% and 95%, thus demonstrating the low reliability of these criteria [2–4, 6, 21–23] and their quite unsatisfactory performance when applied in a routine care setting.

Lacking validated and unequivocal biomarkers for an accurate attribution of the NP events occurring during the course of SLE, the clinical judgement of trained clinicians remains the most reliable tool [18, 22, 24]. In an attempt to overcome this critical point and to assist clinicians in the diagnostic process, we have developed and validated a new algorithm aimed at determining the attribution of NP events occurring in SLE patients.

The algorithm was constructed on a training cohort of SLE patients and then validated on an independent external multicentre cohort. When compared with expert clinical judgement, assumed as the reference standard, it demonstrated good performance in terms of sensitivity, specificity, PPV and NPV, which could be attributed with a confident assumption of correctness at $\sim 33\%$.

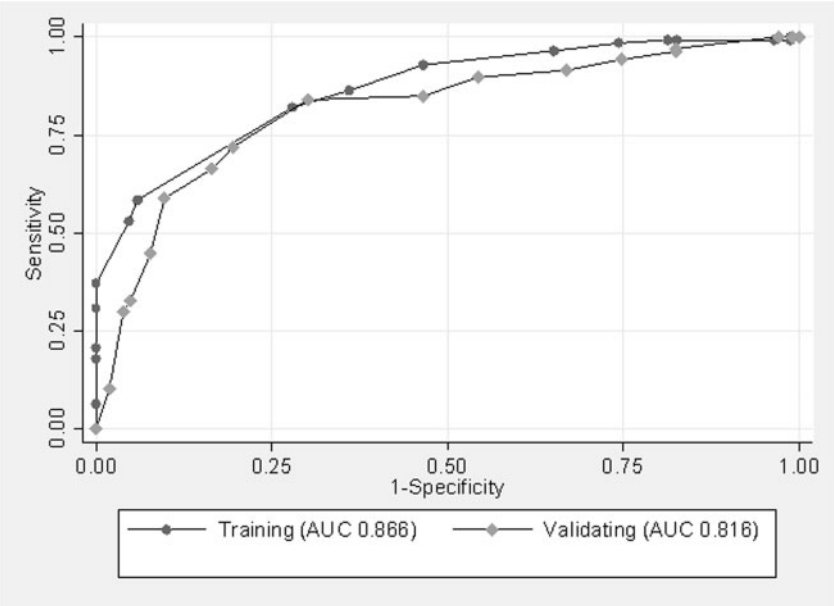
A similar attempt, which inspired our study, was previously conducted by Hanly *et al*. [4, 22, 25], who proposed an attribution model—with a different level of stringency—based on three simple rules that take into account the temporal relationship between the NP event and the diagnosis of SLE, the type of NP event and a comprehensive list of exclusions/associations according to ACR nomenclature. This model was applied in the large SLICC International Multicenter Disease Inception Cohort in a time frame of 10 years from 2004 to 2013 [7, 26–28]. Depending on the set of rules applied (more or less stringent), the proportion of NP events attributable to SLE in a cohort of 1732 patients, of whom 788 had at least one NP manifestation for a total of 1455 events, varied between 16.8% and 30.5%. The latter percentage is similar to the one we found. Another available attempt is that proposed by Monov and Monova [19]. This approach demonstrated

Table 4 A priori, data-driven (ordinal logistic) and updated rescaled coefficients

Variable	Category	A priori coefficient	Data-driven coefficient (95% CI)	Updated coefficient
Time	0 = before	0	0	0
	1 = after	2	0.91 (−0.25, 2.08)	1.5
	2 = concurrent	3	1.54 (0.22, 2.86)	2.5
Major[a]	0 = no	0	0	0
	1 = yes	3	4.82 (3.32, 6.32)	3
Confounders (*n*)	0 ⩾ 1	0	0	0
	1 = 1	1	1.56 (−0.02, 3.15)	1
	2 = 0	2	3.83 (2.13, 5.54)	2.5
Favouring factors (*n*)	0 = 0	0	0	0
	1 = 1	1	0.72 (−0.28, 1.72)	1
	2 ⩾ 1	2	1.98 (1.04, 2.91)	2

[a]If a major criterion was checked as no, that implies that a minor event, as defined in the text, was identified.

Fig. 1 Performance of the classification criteria in the training and validating cohorts



The area under the curve (AUC) of the receiver operating characteristic (ROC) curve using dichotomous outcomes (related *vs* possible/unrelated) showed the following values: 0.866 in the training cohort and 0.816 in the validating cohort.

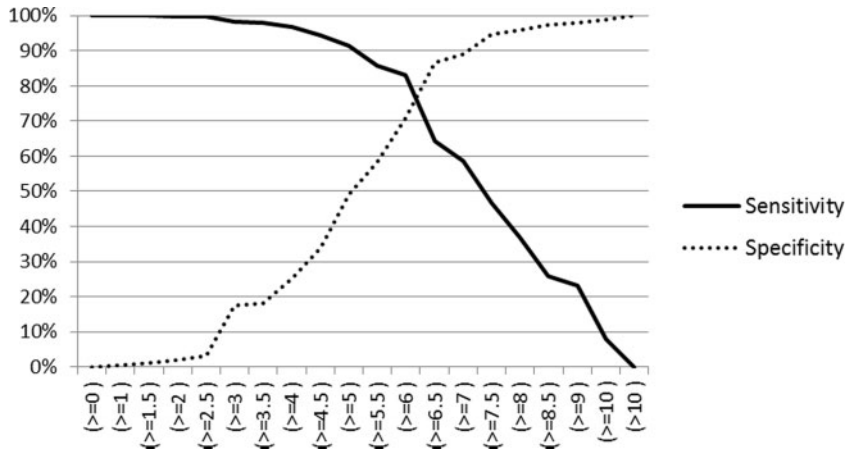
a sensitivity of 90.3%, specificity of 67.7%, a PPV of 70.6% and an NPV of 89.1%.

One of the innovative aspects of our study consists in the inclusion of a new item into the algorithm, corresponding to a careful evaluation of a number of potentially favourable or risk factors that could contribute to guiding the attribution process. A second important contribution of our study is the assignment of a numerical score to each selected item and its corresponding subheading, yielding a global score ranging from 0 to 10, where the greater the global score, the higher the probability that the NP event could be attributed to SLE.

In the definition of the optimal cut-off points to classify an NP event as related (>7) or not related (<3) to SLE, the criterion adopted was aimed at minimizing misclassification to <10%, which was deemed clinically acceptable, given the complexity of the NP involvement.

Our study has some limitations. A first critical point consists of a potential referral bias, since the recruitment from tertiary centres could have selected those patients with more severe disease, not fully representing the entire spectrum of the disease. Linked to this point, a second important limitation depends on the low number of some rare NP events retrieved in both the training and validating cohorts, making the results not fully generalizable to all the NP events included in the ACR glossary. Finally, circular thinking might have inflated the accuracy of the model, as the experts might have selected those items

FIG. 2 Graph of sensitivity and specificity *vs* cut-offs



Based on the receiver operating characteristic (ROC) table on a dataset combining the training and validating samples, the best single cut-off was $\geqslant 6$, with sensitivity 83% (95% CI 77.7, 87.5) and specificity 70.9% (95% CI 63.9, 77.3).

they use in their practice to attribute NP manifestations to SLE. However, fully independent external validation involving a qualified subinvestigator who had not taken part in the construction of the algorithm should have reduced the impact of this potential bias.

It should be pointed out that this algorithm—in its actual format—is not intended as a substitute for clinical judgement, which still remains the cornerstone of the diagnosis and management of NPSLE. Consistent with this assumption is the persistence of a wide and probably non-resettable grey area of uncertainty in the attribution process that reflects both the complexity of the issue we are facing and the lack of a reliable marker for the attribution process itself.

In conclusion, our algorithm represents a new robust and potentially useful tool that can be used for research and also to assist the clinician when dealing with NP involvement in SLE, thus enabling the identification of which NP events have a high probability of being or not being attributed to the disease among SLE patients and doing it in a more standardized and reproducible manner than before.

Rheumatology key messages

- The relationship linking a neuropsychiatric event with SLE remains a critical issue.
- Timing and type of neuropsychiatric event, confounding factors and favouring factors should be considered when assessing neuropsychiatric SLE.
- The attribution algorithm represents an improvement in assessment of neuropsychiatric SLE patients.

Acknowledgements

M.P. gratefully acknowledges the Sardinia Regional Government for its financial support (P.O.R. Sardegna F.S.E. Operational Programme of the Autonomous Region of Sardinia, European Social Fund 2007–2013—Axis IV Human Resources, Objective l.3, Line of Activity l.3.1).

Disclosure statement: G.F. has received research support from BMS and Roche and honoraria from AbbVie, MSD, Pfizer, UCB and Roche. All other authors have declared no conflicts of interest.

Supplementary data

Supplementary data are available at *Rheumatology* Online.

References

1 The American College of Rheumatology nomenclature and case definitions for neuropsychiatric lupus syndromes. Arthritis Rheum 1999;42:599–608.

2 Ainiala H, Hietaharju A, Loukkola J *et al*. Validity of the new American College of Rheumatology criteria for neuropsychiatric lupus syndromes: a population-based evaluation. Arthritis Rheum 2001;45:419–23.

3 Ainiala H, Loukkola J, Peltola J, Korpela M, Hietaharju A. The prevalence of neuropsychiatric syndromes in systemic lupus erythematosus. Neurology 2001;57:496–500.

4 Hanly JG. ACR classification criteria for systemic lupus erythematosus: limitations and revisions to neuropsychiatric variables. Lupus 2004;13:861–4.

5 Sibbitt WL Jr, Brandt JR, Johnson CR *et al*. The incidence and prevalence of neuropsychiatric syndromes in pediatric onset systemic lupus erythematosus. J Rheumatol 2002;29:1536–42.

6 Brey RL, Holliday SL, Saklad AR *et al*. Neuropsychiatric syndromes in lupus: prevalence using standardized definitions. Neurology 2002;58:1214–20.

7 Hanly JG, Urowitz MB, O'Keeffe AG *et al*. Headache in systemic lupus erythematosus: results from a prospective, international inception cohort study. Arthritis Rheum 2013; 65:2887–97.

8 Linstone HA, Turoff M. The Delphi Method. Reading, MA, USA: Addison-Wesley, 1975.

9 Jones J, Hunter D. Consensus methods for medical and health services research. BMJ 1995;311:376–80.

10 Hochberg MC. Updating the American College of Rheumatology revised criteria for the classification of systemic lupus erythematosus. Arthritis Rheum 1997;40: 1725.

11 Bombardier C, Gladman DD, Urowitz MB, Caron D, Chang CH. Derivation of the SLEDAI. A disease activity index for lupus patients. The Committee on Prognosis Studies in SLE. Arthritis Rheum 1992;35:630–40.

12 Govoni M, Bombardieri S, Bortoluzzi A *et al*. Factors and comorbidities associated with first neuropsychiatric event in systemic lupus erythematosus: does a risk profile exist? A large multicentre retrospective cross-sectional study on 959 Italian patients. Rheumatology 2012;51:157–68.

13 Gladman D, Ginzler E, Goldsmith C *et al*. The development and initial validation of the Systemic Lupus International Collaborating Clinics/American College of Rheumatology Damage Index for systemic lupus erythematosus. Arthritis Rheum 1996;39:363–9.

14 Mikdashi J, Handwerger B. Predictors of neuropsychiatric damage in systemic lupus erythematosus: data from the Maryland lupus cohort. Rheumatology 2004;43:1555–60.

15 Tomietto P, D'Agostini S, Annese V, De Vita S, Ferraccioli G. Mycophenolate mofetil and intravenous dexamethasone in the treatment of persistent lupus myelitis. J Rheumatol 2007;34:588–91.

16 Andrade RM, Alarcón GS, González LA *et al*. Seizures in patients with systemic lupus erythematosus: data from LUMINA, a multiethnic cohort (LUMINA LIV). Ann Rheum Dis 2008;67:829–34.

17 Bertsias GK, Ioannidis JPA, Aringer M *et al*. EULAR recommendations for the management of systemic lupus erythematosus with neuropsychiatric manifestations: report of a task force of the EULAR standing committee for clinical affairs. Ann Rheum Dis 2010;69:2074–82.

18 Sciascia S, Bertolaccini ML, Baldovino S *et al*. Central nervous system involvement in systemic lupus erythematosus: overview on classification criteria. Autoimmun Rev 2013;12:426–9.

19 Monov S, Monova D. Classification criteria for neuropsychiatric systemic lupus erythematosus: do they need a discussion? Hippokratia 2008;12:103–7.

20 Bertsias G, Ioannidis JPA, Boletis J *et al*. EULAR recommendations for the management of systemic lupus erythematosus. Report of a Task Force of the EULAR Standing Committee for International Clinical Studies Including Therapeutics. Ann Rheum Dis 2008;67:195–205.

21 Govoni M, Rizzo N, Castellino G, Padovan M, Trotta F. [Neuropsychiatric systemic lupus erythematosus: where are we now?]. Reumatismo 2005;57:215–25.

22 Hanly JG, Urowitz MB, Sanchez-Guerrero J *et al*. Neuropsychiatric events at the time of diagnosis of systemic lupus erythematosus: an international inception cohort study. Arthritis Rheum 2007;56:265–73.

23 Ruggieri AP. Neuropsychiatric lupus: nomenclature, classification, criteria, and other confusional states. Arthritis Rheum 2001;45:406–9.

24 Nived O, Sturfelt G, Liang MH, De Pablo P. The ACR nomenclature for CNS lupus revisited. Lupus 2003;12:872–6.

25 Hanly JG, McCurdy G, Fougere L, Douglas J-A, Thompson K. Neuropsychiatric events in systemic lupus erythematosus: attribution and clinical significance. J Rheumatol 2004;31:2156–62.

26 Hanly JG, Urowitz MB, Su L *et al*. Prospective analysis of neuropsychiatric events in an international disease inception cohort of patients with systemic lupus erythematosus. Ann Rheum Dis 2010;69:529–35.

27 Hanly JG, Su L, Farewell V *et al*. Prospective study of neuropsychiatric events in systemic lupus erythematosus. J Rheumatol 2009;36:1449–59.

28 Hanly JG. Demystifying neuropsychiatric lupus—is it possible? Bull NYU Hosp Jt Dis 2009;67:276–80.