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Original article

Value of multidisciplinary reassessment in attribution of neuropsychiatric events to systemic lupus erythematosus: prospective data from the Leiden NPSLE cohort

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Abstract

Objective. To determine the contribution of reassessment in the attribution process of neuropsychiatric (NP) events to SLE or other aetiologies in a large, prospective and multidisciplinary assessed NPSLE cohort and to compare these results with other available attribution models for NP events occurring in SLE.

Methods. Three hundred and four consecutive SLE patients presenting NP events were evaluated. All subjects underwent standardized multidisciplinary medical, neuropsychological, laboratory and radiological examination on the inclusion and reassessment dates. Diagnosis was always established by multidisciplinary consensus. The final diagnosis after reassessment also took into account disease course and response to treatment. These data were compared with currently available attribution models for NP events in SLE.

Results. A total of 463 NP events were established. After reassessment, attribution to SLE was discordant in 64 (13.8%) NP events when compared with the first visit. We show that 14.5% of NP events previously attributed to SLE reclassified as non-NPSLE. In 86.4% of these patients immunosuppressive therapy was started after the first visit. When reassessment and available attribution models were compared, NPSLE cases overlapped considerably. Although specificity was high for all comparisons (0.81–0.95), an important variation in sensitivity (0.39–0.83) and agreement estimates ($\kappa = 0.29$–0.68) was observed. The Italian algorithm showed the highest sensitivity and specificity (>0.80) and moderate agreement (0.59–0.64).

Conclusion. In clinical practice NP events presenting in SLE are too often attributed to an immune-mediated origin. Multidisciplinary reassessment avoids misclassification in NPSLE. Multidisciplinary reassessment is the reference standard in NP events presenting in SLE and cannot be replaced by available attribution models.

Key words: systemic lupus erythematosus, neuropsychiatric systemic lupus erythematosus, NPSLE, attribution, multidisciplinary approach

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CLINICAL SCIENCE

Rheumatology key messages

- Multidisciplinary clinical assessment is useful to attribute neuropsychiatric events to SLE or to other aetiologies
- Reassessment is key to avoid misclassification in attribution of neuropsychiatric events in SLE.
- Until we find more reliable tests, reassessment will remain as reference standard in neuropsychiatric SLE diagnosis.

Introduction

Neuropsychiatric SLE (NPSLE) is a term encompassing a broad and heterogeneous group of neuropsychiatric (NP) symptoms that are the consequence of the involvement of the nervous system due to SLE. The presentation of an NP event in a patient with SLE represents a well-known diagnostic challenge [1]. So far, there is neither a gold standard nor a single complementary test that specifically discriminates between SLE-related and SLE-unrelated NP events. Consequently, in clinical practice, NPSLE is a diagnosis *per exclusionem*, requiring an extensive differential diagnosis orientated to the presenting NP event.

The final attribution of NP events to SLE is a crucial issue since it has important implications for management and prognosis. A small number of studies have rigorously analysed the attribution of NP events to SLE. Hanly *et al.* [2, 3] reported that only one-third of all NP events presented in a large SLE cohort were directly attributable to SLE; however, differences in the reported prevalence of NPSLE vary widely (15–91%) due to different study designs among reports and more importantly due to the diverse interpretation of NPSLE definitions [4]. For example, the nomenclature published by the ACR, the most comprehensive attempt to define NP manifestations in SLE patients, includes minor NP events (e.g. headache); these are known to be non-specific and to some degree investigator dependent [5–9]. In an attempt to assist physicians, some attribution models for NP events occurring in SLE have been previously proposed. Despite the merits of these approaches [2, 3, 6, 10, 11], in clinical practice, expert physician judgement based on clinical and complementary tests remains so far the most appropriate reference standard for NPSLE diagnosis [12].

In SLE patients presenting for the first time with an NP event, recognizing an SLE-related origin can be difficult, and sometimes the diagnosis of NPSLE will be presumptive. Reassessment of NPSLE patients may be thus of paramount importance in the attribution process. At a follow-up visit, the clinical course and the response to therapy harbour crucial information that will help in the attribution of NP events to SLE or other aetiology [13–15]. To the best of our knowledge, the value of reassessment of NP events in SLE patients has never been addressed before and it is unknown how the evaluation over time may provide insight into this complex and important aspect of SLE.

The aim of the present study is therefore (i) to determine the contribution of reassessment in the attribution of NP events to SLE or to other aetiologies in a large, prospective and multidisciplinary assessed SLE cohort. Assuming that the course of disease leads to a putative reference standard, this also allows us (ii) to assess the accuracy of the first visit and compare these results with all available attribution models for NP events occurring in SLE.

Methods

Subjects

Our study group comprised patients with SLE and NP events from the Leiden NPSLE cohort. Our institution, the Leiden University Medical Centre (The Netherlands), is a national tertiary referral centre for NPSLE where patients are evaluated in a multidisciplinary, standardized and prospective manner. Between September 2007 and March 2016, a total of 304 consecutive patients who were suspected by a referral doctor of having NPSLE were evaluated. The local medical ethics committee, Commissie Medische Ethiek LUMC, approved the study and all patients signed informed consent.

Multidisciplinary assessment

All subjects included in our NPSLE cohort were admitted for a 1-day period and underwent standardized multidisciplinary assessment. In a small number of cases, this evaluation took place during a regular clinical admission in our centre. During the first visit all patients were assessed by specialists in rheumatology, neurology, psychiatry and vascular medicine. In addition, neuropsychological testing, extensive laboratory tests and a 3-tesla MRI of the brain were routinely performed. Additional cerebrospinal fluid analysis, electromyogram, electroencephalogram, evoked potentials, MRI of the spine or MR angiography were performed when indicated. For a detailed description of the evaluations included in the clinical assessment, neuropsychological test battery, laboratory tests and MRI-scanning protocol, see reference [15]. Among the socio-demographic and clinical variables obtained were age, gender, disease duration and activity, lag time between SLE diagnosis and NP event presentation and therapies used before and after the first visit. All patients were classified according to the ACR 1982 revised criteria for SLE [16, 17]. SLE disease activity was calculated with the SLEDAI 2000 [18, 19].

Consensus meeting

The final attribution of NP events to SLE or other aetiologies was made by multidisciplinary consensus after the clinical, serological and neuroimaging assessments and evaluation of neuropsychological status and competing co-morbidities. All medical specialists met in a 2-weekly scheduled meeting to discuss the patients. In acute cases where a prompt therapeutic decision was needed an extra meeting was planned. As described by Zirkzee *et al.* [15], during the consensus meeting the following aspects were

taken into account to determine the origin of NP events: objective confirmation of symptoms (assessed to standard of care of the appropriate medical specialty); exclusion of other aetiology explaining these symptoms; NP event possibly explained by SLE. All identified aetiologies for NP events and the NPSLE definitions were defined, but not restricted, according to those alternative diagnoses and the NPSLE definitions included in the 1999 ACR nomenclature [5]. Since a patient may present several NP events due to different aetiologies, we have chosen to analyse every NP event individually instead of per patient. We also identified the so-called minor NP events as defined by Ainiala *et al.* [7, 9] including headache, anxiety, mild depression, mild cognitive impairment and polyneuropathy without electrophysiological confirmation. Each NP event was attributed to one of the following groups: NPSLE or NP events directly related to SLE, undefined NPSLE when we were not able to either find another aetiology or clearly associate the symptoms with SLE, and non-NPSLE or NP events better explained by other aetiology. Furthermore, non-NPSLE events were divided into the next subgroups: due to primary NP disease, due to medication or drugs, due to a complication of SLE (e.g. strokes following Libman–Sacks endocarditis) and due to other concomitant disease. After the attribution process, the group of specialists made a therapeutic decision per NP event: initiate immunosuppression therapy, secondary prevention, optimize symptomatic therapy, start psychotherapy or stop a specific therapy when the NP event was thought to be medication related. NP events classified as undefined NPSLE where treated with intensive symptomatic therapy while a subset of NP events classified as NPSLE not responding to a previous appropriate symptomatic therapy received a trial with immunosuppressive therapy [10, 13, 15]. All patients included in this group received glucocorticoids (0.5–1 mg/kg/day) and concomitant AZA or MMF. We decided the date of the reassessment depending on the NP event, severity and therapy established. The referral doctors closely followed all patients until the follow-up visit.

Follow-up visit

Reassessment of patients took place 3–18 months after the first visit. Several NP events included in the group non-NPSLE were not reassessed when they were clearly explained by other disease (e.g. cerebral tumour). Patients were again admitted for a 1-day period and underwent the same multidisciplinary assessment as during the first visit. All patients were reassessed by the same specialists. Moreover, neuropsychological battery testing, laboratory and radiological examination using the same protocol were performed and compared with previous tests. For a further description of multidisciplinary assessment and performed tests at this point see reference [15]. Two weeks after reassessment a consensus meeting took place and the following factors were taken into account for every NP event: evolution over time and evaluation of improvement or worsening of previous evaluated NP events; onset of new NP events or other symptoms related and non-related to SLE that may explain or contribute to new and previous NP events. NP events better explained by other aetiologies were divided into the same groups as described after the first visit.

Other attribution models

Three different models for the attribution of NP events to SLE have been proposed. The SLICC group developed two different models with different stringency (model A more stringent and B less stringent) taking into account the temporal relationship between the NP event and SLE diagnosis, the presence of exclusions or associations described in the 1999 ACR nomenclature and whether the NP event was one of the minor NP events described by Ainiala *et al.* [2, 5, 7, 9]. Attribution of an NP event to SLE by the SLICC attribution model A (SLICC-A) included the following: NP event onset from 6 months prior to 15 months after SLE diagnosis, was not a minor NP event and exclusions or associations as described in the ACR nomenclature were not present; and in the case of SLICC attribution model B (SLICC-B): NP event onset within 10 years from SLE diagnosis, was not a minor NP event and exclusions as described in the ACR nomenclature were not present.

Recently, the Italian study group on NPSLE proposed an algorithm for the attribution of NP events to SLE based on a probability score [10]. This model addresses: temporal relationship of NP events to SLE diagnosis; identification of minor NP events; recognition of confounding factors as described in the ACR nomenclature for NPSLE; and favouring factors including the specific SLE-related risk factor derived from the EULAR recommendations on NPSLE and other further information considered of importance for the group [10, 20]. The authors proposed two cut-off points in a scale from 0 to 10 points. NP events with a score of <3 were considered to be due to non-SLE causes, between 3 and 6 as undefined, and 7 or more as due to SLE [10].

Statistical analysis

SPSS Statistics for Windows version 20.0 (IBM Corp., Armonk, NY, USA) was used for analysis. Differences between qualitative variables were assessed using the chi-square test. Sensitivity, specificity, positive predictive value and negative predictive value for reassessment against the other attribution models and first visit were determined. We assumed that the course of every NP event leads to a putative reference and subsequently we used the final attribution after multidisciplinary reassessment as gold standard. We also analysed the performance of the attribution models when compared with the first visit. In the case of the first visit and the Italian algorithm we used dichotomous outcomes, including undefined and non-NPSLE in the same group. Agreement between reassessment, first visit and other attribution models was calculated with the use of Cohen's kappa (K) measures of agreement.

Results

Patients' characteristics

A total of 304 SLE patients were evaluated. The median age of all patients at the time of the study was 42.5 years [interquartile range (IQR): 33–50 years] and 89.7% were female. The median duration of SLE was 4.6 (IQR: 1.2–13.2) years; in 11 patients we were not able to establish an NP diagnosis at the first visit. The rest of the 293 patients were diagnosed with at least one NP event; a total of 463 NP events were established. Table 1 shows the attribution of all 463 NP events after the first visit. The median number of NP events presented in all NPSLE patients was 1 (IQR: 1–2; range 1–5). NPSLE patients also presented 26 concomitant NP events non-attributed to SLE and 9 NP events classified as undefined. NP events attributed to SLE developed after a median of 1.9 (IQR: 0.2–11.6) years. A total of 65 (42.8%) NP events attributed to SLE presented in the first year after SLE diagnosis. In 37 of these 65 NP events, NPSLE was diagnosed at the same time as SLE. Figure 1 shows all 463 NP events distributed according to attribution at first visit and reassessment. Besides Guillain-Barre syndrome and myasthenia gravis, all ACR definitions were represented in our cohort. Among all the NP events, a total of 224 were identified as minor NP events [7, 9]. In our cohort, a low number of NP events diagnosed as headache (4/79; 5.1%), mood disorder (9/88; 10.2%), cognitive dysfunction (19/72; 26.3%) or anxiety (2/22; 9.1%) were attributed to SLE.

Table 1 Attribution of neuropsychiatric events at first visit and after reassessment

Attribution first visit	Attribution reassessment		
	Non-NPSLE	NPSLE	Total
Non-NPSLE			
Count	269	6	275
% total	58.1	1.3	59.4
NPSLE			
Count	22	130	152
% total	4.8	28.1	32.8
Undefined			
Count	27	9	36
% total	5.8	1.9	7.8
Total			
Count	318	145	463
% total	68.7	31.3	100.0

NPSLE: neuropsychiatric SLE.

Comparison between first visit and reassessment

The final attribution of NP events to SLE or other aetiologies after reassessment was analysed (Table 1). Most of the patients were reassessed 6 (IQR: 4–12) months after the first visit. Of the 152 NP events attributed in the first to SLE, a total of 22 (14.5%) were reclassified to the non-NPSLE group. Of these 22 NP events, in 19 (86.4%) an immune-mediated origin of the symptoms was suspected at first visit and immunosuppressive therapy was started. A further description of NP events re-included in the NPSLE group after reassessment is available in Supplementary Table S1, available at *Rheumatology* Online. On the other hand, of the 275 NP events previously related to non-SLE aetiologies, only 6 NP events (2.2%) were reclassified into the NPSLE group (see Fig. 2 for flow chart of NP events). In total, there were 64 (13.8%)

Fig. 1 Summary of NP events (n = 463) after the clinical judgement at first visit and reassessment

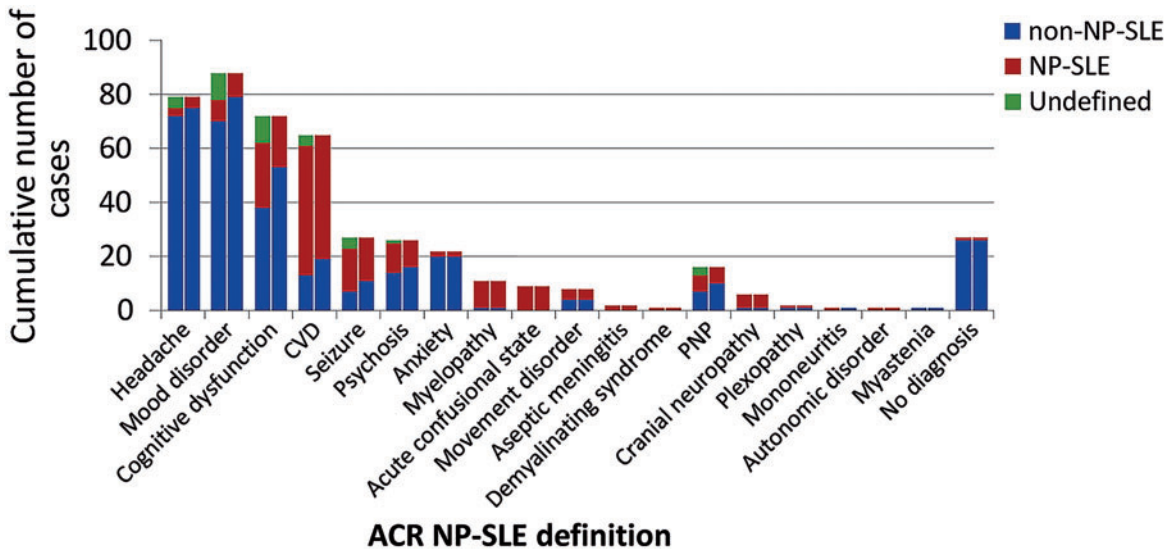
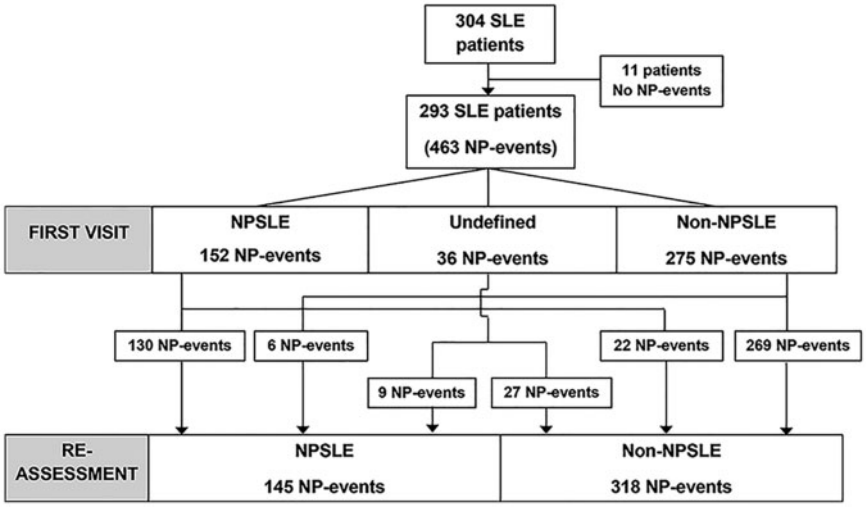


Fig. 2 Flow chart of NP events presented in the Leiden NPSLE cohort



discordant NP events when the first visit and reassessment were compared. Agreement between the first visit and reassessment was very good ($\kappa = 0.82$). After reassessment, among the 318 NP events non-attributed to SLE, a total of 217 were better explained by other primary NP aetiology, 39 NP events were attributed to medication or drugs, 26 due to a concomitant non-NP disease, 10 were related to an SLE complication and in 26 NP events we were not able to establish a diagnosis included in the ACR nomenclature. A summary of all alternative diagnosis in the non-NPSLE group is available in Supplementary Table S2, available at *Rheumatology* Online.

Response to therapy and reclassification

A total of 36 NP events were categorized after the first visit as undefined NPSLE and subsequently treated with intensive symptomatic therapy. After reassessment these NP events reclassified into NPSLE (9 NP events) and non-NPSLE (27 NP events). Furthermore, a total of 28 NP events attributed to SLE not responding to a previous appropriate symptomatic therapy received a trial of immunosuppressive therapy after the first visit. After reassessment 19 NP events had a favourable response and were definitely attributed to SLE while 9 NP events did not respond and were thought to be non-SLE related.

Comparison and agreement with other attribution models

The number of NP events attributed to SLE varied considerably when the different attribution models were used (Table 2). Of all NP events, a total of 38 (8.2% of the total NP events) and 243 were, respectively, attributed to SLE or to other aetiology by all the different attribution approaches. When compared with the reassessment, specificity was high for all models (0.81–0.95) while sensitivity changed importantly depending on the models analysed (0.29–0.81). Comparable results were found when first visit was used as reference and compared with all attribution models. Positive predictive value was low when attribution models were compared with reassessment (0.65–0.75) while negative predictive value was higher (0.75–0.90). A very low sensitivity was specially marked for SLICC-A due to the small number of NP events attributed to SLE. When compared with first visit and reassessment, the Italian model showed a reasonably high

Table. 2 NP events attributed to SLE at the first visit and reassessment and according to different attribution models

	Non-NPSLE	First visit	Reassessment	SLICC-A	SLICC-B	Italian algorithm
Non-NPSLE	243	311	318	407	324	287
First visit	311	152[a]	130	50	97	126
Reassessment	318	130	145[a]	42	90	117
SLICC-A	407	50	42	56[a]	56	52
SLICC-B	324	97	90	56	139[a]	124
Italian algorithm	287	126	117	52	124	176[a]

[a]Number of NP events attributed to SLE. NPSLE: neuropsychiatric SLE.

TABLE 3 Accuracy indexes, predictive values and Cohen's kappa measures of agreement between neuropsychiatric SLE diagnosis and attribution models

	Sensitivity (95% CI)	Specificity (95% CI)	PPV (95% CI)	NPV (95% CI)	Kappa (95% CI)
Reassessment/first visit[a]	0.89 (0.83, 0.94)	0.93 (0.89, 0.96)	0.85 (0.79, 0.91)	0.95 (0.92, 0.97)	0.82 (0.76, 0.87)
Reassessment/SLICC-A	0.29 (0.22, 0.37)	0.95 (0.93, 0.98)	0.75 (0.62, 0.86)	0.75 (0.70, 0.79)	0.29 (0.21, 0.38)
Reassessment/SLICC-B	0.62 (0.54, 0.70)	0.85 (0.80, 0.88)	0.65 (0.56, 0.73)	0.83 (0.78, 0.87)	0.47 (0.38, 056)
Reassessment/Italian algorithm	0.81 (0.73, 0.87)	0.81 (0.76, 0.86)	0.66 (0.59, 0.73)	0.90 (0.86, 0.93)	0.59 (0.51, 0.66)
First visit/SLICC-A	0.33 (0.25, 0.41)	0.98 (0.96, 0.99)	0.89 (0.78, 0.96)	0.75 (0.70, 0.79)	0.37 (0.28, 0.45)
First visit/SLICC-B	0.64 (0.56, 0.71)	0.86 (0.82, 0.90)	0.70 (0.61, 0.77)	0.83 (0.78, 0.87)	0.51 (0.43, 0.60)
First visit/Italian algorithm	0.83 (0.76, 0.88)	0.84 (0.79, 0.88)	0.72 (0.64, 0.78)	0.91 (0.87, 0.94)	0.64 (0.57, 0.71)

[a]First group in the first column indicates the group used as reference standard. NPSLE: neuropsychiatric SLE; NPV: negative predictive value; PPV: positive predictive value.

sensitivity (0.83 and 0.81, respectively), specificity (0.84 and 0.81, respectively) and NPV (0.91 and 0.90, respectively). The agreement was good when the Italian algorithm was compared with the first visit and reassessment ($\kappa = 0.64$ and 0.59, respectively). Among the rest of the comparisons, the agreement was poor to moderate (Table 3).

Discussion

To the best of our knowledge, this is the first study where a large cohort of SLE patients presenting NP events is evaluated in a prospective manner by a multidisciplinary team. We have been able to characterize 463 NP events occurring in 293 SLE patients using this multidisciplinary assessment and to follow the evolution of NP events over time.

We show that reassessment of NP symptoms in SLE reclassifies a total of 13.8% of NP events. Interestingly, of all NP events first misdiagnosed as NPSLE, 86.4% were attributed to an immune-mediated origin and received immunosuppression. Our data suggest that, in clinical practice, over-diagnosis related with an immune-mediated origin is more common than under-diagnosis in NPSLE. This demonstrates the complexity and the difficulties found in clinical practice to reach an accurate diagnosis at the first visit. There was an acceptable interrater agreement between the two visits, which may have different interpretations. Diagnosis during first visit seems accurate since we were able to identify the majority of real non-NPSLE and NPSLE events. However, we think that having 64 (13.8%) NP events with an incorrect attribution after the first visit is a serious problem and stresses the fact that new and more reliable tests for NPSLE are urgently needed [21]. Until those tests are available, it will be very likely that we over-diagnose NPSLE in SLE patients presenting with NP events. Therefore, we believe that multidisciplinary reassessment is so far the most accurate approach to attribute NP events to SLE. Furthermore, this increasing of diagnostic accuracy in NPSLE may have important consequences not only in individual patients but also for studies of physiopathology mechanisms and therapy trials.

We have analysed the role of the response to therapy in the attribution of NPSLE. After reassessment, and subsequently after receiving intensive symptomatic therapy, we were able to establish a final diagnosis for all NP events categorized as undefined NPSLE in the first visit. Furthermore, in 14.6% of the NP events attributed to SLE after the first visit, the final diagnosis could only be confirmed after evaluating the response to a trial of immunosuppressive therapy. Our findings demonstrate the importance of monitoring the evolution of NP events and their response to specific therapeutic interventions in the attribution process of NP events to SLE.

We have been able to describe and divide into four different groups the alternative aetiologies explaining the NP events other than SLE. The diagnosis of other primary NP disease accounts for 68.2%. Among them a total of 88.9% of NP events correspond to minor NP events [7, 9]. The presence of these minor NP events is known to substantially influence the prevalence of NPSLE [4]. Although minor NP events were considered the most prevalent NPSLE events in the past, definitions have evolved over time as has medical knowledge; in past years there has been a tendency to consider that in most of these minor NP events there is no subjacent immune-mediated origin [8, 9, 13, 22, 23]. Our data confirm the low rate of SLE-attribution for these minor NP events and point out the importance of an exhaustive differential diagnosis and the need for a more stringent approach to attribute NP events to SLE.

We have compared different accepted attribution models for NP events presented in SLE patients. We demonstrated the important variation in frequency and agreement estimates and how NPSLE diagnosis overlaps considerably. The high specificity and NPV and on the other hand the wide variability in sensitivity indicate that all attribution models recognize reasonably well non-NPSLE events, while the recognition of NP events associated to SLE is more problematic. These data show that available attribution models are more useful for the exclusion of NPSLE than for its recognition. The high specificity

and the low sensitivity and agreement of SLICC-A respond to the strict requirements of this model. Two factors have a substantial influence in these results: the stringent enrolment window; and the exclusion of a patient as NPSLE when recognizing non-SLE variables (e.g. coexistent conditions or drugs) as having contributed in part to the NP event, the so-called associations [2]. The SLICC-B model, a less strict model, showed a moderate sensitivity and agreement. Of note, the Italian algorithm showed an acceptable sensitivity and specificity, a high NPV and good agreement when compared with the first visit and reassessment. Recently, a retrospective study has shown similar results [24]. Our data show that this method performs reasonably well with both the first visit and reassessment and may be a reliable tool for research matters; however, as already acknowledged by the authors, we believe that this algorithm should not be used as a substitute for clinical judgement [10].

There are limitations in this study. Our study shares with other studies a heterogeneous and small frequency of certain NPSLE syndromes. This avoids drawing firm conclusions about how reassessment may affect specific NPSLE syndromes; however, our cohort is formed by patients referred from all over the country and covers a large part of the NPSLE spectrum, which may lead to a more real-life setting, thereby diminishing confounding and allowing for the generalizability of our results. Among many other factors, the attribution at first visit was taken into account to reach a final decision at reassessment, which may have led to incorporation bias and subsequently to an overestimation of test accuracy for the first visit when compared with other attribution models. Nevertheless, our study is based in a clinical setting. At reassessment, it is imperative to know the attribution at first visit to know if a certain NP event has been misclassified. Although unlikely, the possibility that at reassessment an NP event improved due to the waxing and waning nature of SLE rather than to a good response to anti-inflammatory therapies cannot be excluded. Another limitation may be the variance in follow-up intervals. Reassessment was scheduled after 6–18 months for most of the patients. These intervals were chosen because we are used to giving courses of anti-inflammatory therapy for at least 6 months and sometimes extend these to 18 months (e.g. cyclophosphamide). Furthermore 6 months seems enough time to evaluate the effect of symptomatic therapies (e.g. anti-depressive therapy). Although patients were closely followed by referral doctors, we do not know how additional information from in-between visits could have yielded valuable information about the evolution of NP events.

In summary, this is the first study evaluating the effect of reassessment of NP events presented in a large prospective SLE cohort. Our data show that multidisciplinary clinical assessment is useful to attribute NP events to SLE or to other aetiologies; however, NPSLE may be over-diagnosed and too often attributed to an immune-mediated origin. Reassessment helps to avoid misclassification in attribution of these NP events to SLE. Evaluating the response to empirical therapies in certain subsets of patients is a key element at this point. Existing attribution models for NPSLE cannot replace clinical judgement; however the Italian algorithm is relatively accurate and a potential tool to be used for research matters. Until we have more reliable serological or radiological biomarkers, we recommend multidisciplinary reassessment as the standard of care in SLE patients presenting NP events.

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Supplementary data

Supplementary data are available at *Rheumatology* Online.

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