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Editorial

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Lupus or not lupus? Neuropsychiatric symptom attribution in systemic lupus erythematosus

Repetita iuvant

SLE is always a rather complex disease. NPSLE can have a wide variety of manifestations, ranging from seizures to neuropathy and from psychosis to stroke. None of these manifestations is so specific to be unequivocally linked to the underlying disease [1]. In this issue, Magro-Checa *et al.* [2] investigate how different approaches perform in attributing neuropsychiatric (NP) symptoms to the underlying SLE.

Since the publication of the 1999 ACR standard nomenclature and case definition [3], some studies have led to the development of different attribution models [4–6]. Two of these [5, 6] have been tested in an independent retrospective study [7]. The first is the SLICC model [5], which includes simple rules with different levels of stringency (models A and B) that consider the temporal relationship between the NP event and the diagnosis of SLE, the type of NP event (defining minor NP events [8] as not attributable to SLE) and a comprehensive list of exclusions/associations according to the ACR nomenclature. Depending on the set of rules applied, the proportion of NP events attributable to SLE varies between 16.8% (model A) and 30.5% (model B).

The second model, by the Italian Study Group for NPSLE (on behalf of the Italian Society of Rheumatology), developed new attribution rules based on a simple numerical algorithm yielding a probability score [6]. The algorithm includes four items, three of which are provided by the SLICC model plus a new one, called favouring factors. This latter item was intended to aid the decision process by checking a list of demographic, clinical, laboratory and imaging information that could support attribution to SLE, derived from the EULAR recommendations on NPSLE [9] and expert panel opinion. The sum of weighted items generates a normalized score ranging from 0 to 10. Overall, the model demonstrated good performance allowing attribution to SLE, with >90% post-test probability in about one-third of NP events.

Recently, Tay and Mak [10] reviewed this topic and created a flow chart in order to reach a confident attribution of NP events in SLE patients. The first step requires satisfying the 1999 ACR filter to exclude NP conditions generated by aetiologies other than SLE, the second step consists of the exclusion of minor events included in Ainiala *et al.*'s list [8] and the third step contemplates the application of favouring factors provided by the Italian algorithm.

The study of Magro-Checa *et al*. [2] adds new information to this scenario, including 293 SLE patients from the Leiden cohort presenting with NP events. The patients underwent a standardized multidisciplinary assessment at presentation and after an average of 6 months. The authors also took disease course and responses to therapy into consideration. This final clinical judgement served as a gold standard by investigating the performance of the first evaluation as well as the SLICC and Italian Society of Rheumatology attribution rules [5, 6]. At the first visit, each NP event was clinically defined as an NPSLE event, undefined event or non-NPSLE event. Based on this, the multidisciplinary team adopted a therapeutic decision, ranging from optimization of symptomatic therapy to immunosuppressive treatment. The study analysed a total of 463 NP events according to type. At the first visit, 32.8% of NP events were classified as NPSLE and at reassessment this percentage changed slightly to 31.3%. After reassessment, attribution to SLE was discordant in 64 (13.8%) NP events when compared with the first visit. Of NP events previously attributed to SLE, 14.5% were reclassified as non-NPSLE and 86.4% of these were treated with immunosuppressive therapy. Conversely, only 2.2% of NP events previously assigned as non-NPSLE were reclassified as NPSLE at reassessment. When the available attribution models were then tested against this gold standard, specificity was acceptable for all rules (0.81–0.95), but sensitivity varied (0.29–0.83). The κ values for agreement with the final diagnosis were 0.82 for the authors' own clinical diagnosis, 0.59 for the Italian attribution rules and 0.47 for the performance of the two SLICC attribution models.

As in previous studies [5, 6] and in the Leiden cohort, less than one-third of NP events were deemed SLE related, indicating that only these could be confidently attributed to the disease. This low proportion should be taken into account when defining the burden of NPSLE. Some rare NP events were little or not at all represented, making the value of the reassessment strategy not entirely pertinent to all the NP events included in the ACR glossary. After reassessment, more NP events previously classified as NPSLE were reassigned to the non-NPSLE group than vice versa. These patients had typically received a trial of immunosuppressive therapy and so there was a risk of overtreatment and related side effects. Another point to consider is that an attribution process based on the retrospective evaluation of response to therapy,

although potentially more accurate, is not meaningful in driving clinical decisions and exploring novel treatments. The scheduled time frame between the first visit and reassessment, ranging from 3 to 18 months (average time of 6 months) appears debatable. Although organizational and economic problems could have contributed to a less well-defined follow-up strategy in the study, and taking into account a discordant rate of 13.8%, closer and tighter control of patients presenting with NP events seems advisable in clinical practice. With regards to the comparison with existing attribution models, from a strictly methodological point of view the reassessment performed by the same multidisciplinary team could have led to a bias that may have inflated the accuracy of the first visit assessment when compared with the other attribution models.

There are several points of strength in the study. First, the reasonability of this approach helped to reproduce a praxis that is usually already adopted in clinical practice, where tight follow-up of patients and evaluation of the responses to therapy are used by clinicians as relevant information to seek attribution. Second, the study also confirmed a satisfactory reliability of the available attribution models, which could be used as a potential tool for research. Finally, this strategy does not miss by default the checking of minor or non-specific NP events that, with low frequency, can be attributed to SLE. However, these kinds of NP events require a rigorous and more stringent approach.

Taking into account the available attribution rules, the glass is at least half full. In addition, it is comforting to note that the issue of attribution is increasingly being taken into consideration by researchers. This fosters hope for the future. Attribution models aided by new biomarkers and advances in neuroimaging will all hopefully improve both diagnostic accuracy and our pathophysiological knowledge of NPSLE.

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