The Pursuit of Precision in Paraneoplastic Neurologic Disease

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In this issue of Neurology® Neuroimmunology & Neuroinflammation, Graus et al. have provided an update to the 2004 paraneoplastic neurologic syndromes (PNS) diagnostic criteria.1,2 Cancer and its remote effects in the body are not a new diagnostic entity. As early as the mid-1800s, Trousseau3 described recurrent thrombophlebitis in association with gastric carcinoma. Nonetheless, over the past few decades, there has been increasing awareness of paraneoplastic syndromes, especially those affecting the nervous system, underscoring the need for clear guidelines to ensure that diagnostic nomenclature is used correctly in both the clinical and research settings.

The authors specifically and appropriately acknowledged confusion around commonly used terminology and decided to move away from using the term “onconeural antibodies”—elimination of this term helps clarify that not all neural autoantibodies are associated with malignancy. The panel instead created 3 new risk categories to stratify autoantibodies and their associated syndromes (high-risk, intermediate-risk, and low-risk phenotypes) which offer more precise terminology when describing these conditions. In addition, these guidelines reinforce that a positive autoantibody result is not a “stand-alone” diagnosis, but rather a piece of supportive data that must always be interpreted in the correct clinical circumstance. The hope is that these guidelines provide improved clinical context for clinicians and specify appropriate malignancy evaluation.

The panel developed a new clinical scoring system called the PNS-Care Score. This calculator provides a level of diagnostic certainty in complicated clinical scenarios. Specifically, the PNS-Care Score encompasses the clinical syndromes in the presence of specific neuronal antibodies and/or cancer. The authors note that the criteria, by design, are rather specific and may underestimate the occurrence of PNS cases. Particularly, the authors wanted to avoid “incidental” antibody associations with commonly encountered malignancies, such as prostate cancer. This article also outlines updated cancer screening recommendations. Previous recommendations suggested screening for malignancy up to 4 years after the diagnosis of PNS.4 In this iteration, the authors recommend screening every 4–6 months for 2 years in patients with high-risk phenotypes/antibodies, with the caveat that the guidelines must be adapted to the individual case. For example, if a woman of reproductive age presents with a relapse of anti-N-methyl-D-aspartate receptor (NMDAR) encephalitis, further screening measures to identify a potential ovarian teratoma are appropriate regardless of the timeframe from the index diagnosis. Clinicians should also be aware of testing limitations (e.g., the limited sensitivity of CT imaging for breast malignancy). The specific screening modality should always be informed by the antibody/phenotype tumor association. Finally, the importance of ensuring all patients follow age-appropriate cancer screening measures—in addition to any specific monitoring dictated by the PNS phenotype—cannot be overemphasized in this population.

We commend the authors for taking a broad, comprehensive approach to these updated criteria. Specifically, the comments on the laboratory technique are an important message for all clinicians who order and interpret these assays. The interpretation of any autoantibody result must be combined with a comprehensive clinical evaluation. Caution should be used when interpreting an autoantibody that has low specificity for PNS, particularly when at low titers.5,6 Furthermore, the recent proliferation of assays of limited or unclear clinical significance can be
is that these updated recommendations will be easier to deploy and subsequently study.

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References
1. Francesc G, Vogrig A, Muñiz-Castrillo S, et al. Updated diagnostic criteria for paraneoplastic neurological syndromes. Neurol Neuroimmunol Neuroinflamm. 2021;8(4):e1014.
2. Graus F, Delattre JY, Antoine JC, et al. Recommended diagnostic criteria for paraneoplastic neurological syndromes. J Neurol Neurosurg Psychiatry. 2004;75(8):1135-1140.
3. Trouseau A. Phlegmasia alba dolens. In: Lectures on clinical medicine, delivered at the Hotel-Dieu, Paris. London: London New Sydenham Society; 1865;5:281–332.
4. Titlelar Mj, Soffritti R, Dalmau J, et al. Screening for tumours in paraneoplastic syndromes: report of an EFNS task force. Eur j Neurol. 2011;18(1):19.e13.
5. Lang K, Pruss H. Frequencies of neuronal autoantibodies in healthy controls; estimation of disease specificity. Neurol Neuroimmunol Neuroinflamm. 2017;4(5):e386.
6. Li Y, Jammoul A, Mente K, et al. Clinical experience of seropositive ganglionic acetylcholine receptor antibody in a tertiary neurology referral center. Muscle Nerve. 2015;52(3):386-391.
7. Graus F, Dalmau J. Paraneoplastic neurological syndromes in the era of immune-checkpoint inhibitors. Nat Rev Clin Oncol. 2019;16(9):535-548.
8. Vogrig A, Gigli GL, Segatti S, et al. Epidemiology of paraneoplastic neurological syndromes: a population-based study. J Neurol. 2020;267(1):26-35.
9. Hebert J, Riche B, Vogrig A, et al. Epidemiology of paraneoplastic neurologic syndromes and autoimmune encephalitis in France. Neurol Neuroimmunol Neuroinflamm. 2020;7(6):e883.