

The Patient Perspective in Encephalitis Research

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Research on autoimmune and infectious encephalitis has made substantial progress in recent years in revealing the pathophysiology of these diseases, establishing robust diagnostic criteria, and developing promising treatment options, with a range of clinical trials currently underway. Outcome measures in studies on autoimmune and infectious encephalitis mainly relied on established and widely used tools such as the modified Rankin Scale (mRS). However, the mRS was developed to assess stroke outcome and has a strong focus on motor symptoms and the degree of dependence in daily activities. For example, approximately 80% of patients with anti-NMDA receptor encephalitis (i.e., the most common autoimmune encephalitis variant) achieve a good outcome 2 years after disease onset when evaluated using the mRS.¹ In contrast to these findings, recent studies show that a majority of patients with anti-NMDA receptor encephalitis suffer from relevant and persistent cognitive impairment, despite mRS scores indicating good or very good recovery.^{2,3} This shows that the mRS fails to detect clinically relevant long-term symptoms in these patients. Indeed, persisting cognitive deficits with their detrimental effect on quality of life are specifically important in the frequently very young patients with encephalitis. More recently, encephalitis-specific scores have been developed, e.g., the CASE score for the clinical assessment of patients with autoimmune encephalitis.⁴ While this score is tailored to symptoms in autoimmune encephalitis, it has a strong focus on acute disease symptoms and is less well suited to capture long-term sequelae.

In addition to long-term cognitive deficits, many patients with encephalitis suffer from fatigue, depression, anxiety, and sleep problems.^{2,3,5,6} The assessment of these symptoms likewise has long been neglected in encephalitis research, but recent studies have started to map their prevalence in patients with encephalitis. In addition, quality of life, functional status, social participation, and the patients' views on their disease are now recognized as important factors that contribute to well-being following severe neurologic diseases such as encephalitis.⁷ These so-called patient-reported outcome measures (PROMs) can be distinguished into generic PROMs (e.g., assessing quality of life or social participation) and disease-specific PROMs (tailored to specific symptoms of a disorder). Frequently, a combination of generic and disease-specific PROMs is used, and they have successfully been applied in a wide range of neurologic disorders including stroke, MS, and Parkinson disease.⁷

In this issue of *Neurology*[®] *Neuroimmunology & Neuroinflammation*, Brenner et al. performed a systematic literature review to identify disease-specific PROMs developed for or validated in patients with encephalitis or encephalopathy.⁸ The authors screened almost 8,000 articles and analyzed more than 100 publications in full text, but identified no study that developed or validated a disease-specific PROM for patients with encephalitis (only one study on hepatic encephalopathy met the inclusion criteria). In a secondary analysis, Brenner et al. identified 46 articles that applied generic PROMs in patients with encephalitis, covering quality of life (e.g., using the Euro-QOL-5D), functioning and community integration (e.g., EBIQ), emotional well-being (e.g., BDI II), sleep (e.g., PSQI), and fatigue (e.g., MFIS).

This tremendous and important work has 2 main implications. First, the failure to identify a validated encephalitis PROM highlights a critical gap in the evaluation of long-term outcome in patients with encephalitis that biases outcome evaluation toward clinician-reported measures. This bias is specifically harmful in patients recovering from encephalitis who frequently suffer

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from symptoms that remain undetected in clinical scales such as the mRS, and thus calls for the development of encephalitis-specific PROMs. Second, the study provides an excellent overview on encephalitis research using generic PROMs that show increased levels of fatigue, depressive symptoms, sleep problems, subjective cognitive impairments, and reduced quality of life, thus clearly demonstrating the need to assess these symptoms in patients with encephalitis. However, these generic PROMs await validation in large international cohorts of patients with encephalitis. In addition, the analysis highlights a major problem in the application of PROMs, i.e., the heterogeneity of applied tools. In principle, an advantage of generic PROMs is the comparability across studies and even across diseases. However, the systematic review by Brenner et al. shows that many different tools were used—for example, quality of life was assessed using 12 different PROMs.

Eventually, a combination of disease-specific and generic PROMs, detailed cognitive assessment, and clinical scores will likely yield the most comprehensive and valid assessment of long-term outcome in patients with encephalitis. The use of established generic PROMs (e.g., BDI-II, PSQI) and standardized cognitive batteries will allow for comparability with other disorders.⁹ To address the lack of standardization of generic PROMs, the NIH-funded Patient-Reported Outcomes Measurement Information System (PROMIS) was initiated.¹⁰ PROMIS offers fixed-length questionnaires and computerized adaptive tests to reliably measure a wide range of patient-reported outcomes. Regarding encephalitis-specific PROMs, the international SAPIENCE (Social and psychological long-term impact of NMDA receptor encephalitis) consortium is currently investigating different PROMs to evaluate long-term outcome in anti-NMDA receptor encephalitis.¹¹ Several national and international patient advocacy organizations are involved in all steps of the study to integrate the perspective of patients and caregivers, including study design, definition of outcome measures, data analyses, and dissemination of results. The results of this initiative might thus provide helpful insights for the development of an encephalitis-specific PROM. Such an encephalitis PROM would need to achieve an internationally high level of acceptance for use in patient care and clinical trials to facilitate a

standardized assessment that is comparable across different studies and patient cohorts. An international collaboration of major encephalitis centers and patient advocacy organizations seems to be a promising way to reach this goal.

For their daily routine, clinical neurologists should keep in mind that fatigue, anxiety, depression, sleep problems, and cognitive deficits are frequent features in recovering patients with encephalitis that can be assessed using generic PROMs in clinical routine until an encephalitis-specific PROM is available.

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