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Putting a Band-Aid on a Broken Leg: Antiseizure Medications Are Inferior to Immune Therapies in Autoimmune Epilepsy

Evaluation of Seizure Treatment in Anti-LGI1, Anti-NMDAR, and Anti-GABABR Encephalitis

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OBJECTIVE: This nationwide cohort study evaluates seizure responses to immunotherapy and antiepileptic drugs (AEDs) in patients with anti-leucine-rich glioma-inactivated 1 (LGI1), anti-NMDA receptor (NMDAR), and anti-gamma-aminobutyric-acid B receptor (GABABR) encephalitis. METHODS: Anti-LGI1, anti-NMDAR, and anti-GABABR encephalitis patients with new-onset seizures were included. Medical information about disease course, AEDs, and immunotherapies used, effects, and side effects were collected. Outcome measures were (1) seizure freedom while using AEDs or immunotherapy, (2) days to seizure freedom from start of AEDs or immunotherapy, and (3) side effects. RESULTS: Of 153 patients with autoimmune encephalitis (AIE; 53 LGI1, 75 NMDAR, 25 GABABR), 72% (n = 110) had epileptic seizures and 89% reached seizure freedom. At least 53% achieved seizure freedom shortly after immunotherapy and 14% achieved seizure freedom while using only AEDs ($P < .0001$). This effect was similar in all types ($P = .0001$; $P = .0005$; $P = .013$, respectively). Median time to seizure freedom from AEDs start was 59 days (interquartile range [IQR]: 27-160), and 28 days from start of immunotherapy (IQR: 9-71, $P < .0001$). Side effects were psychotic behavior and suicidal thoughts by the use of levetiracetam and rash by the use of carbamazepine. Carbamazepine was more effective than levetiracetam in reducing seizures in anti-LGI1 encephalitis ($P = .031$). Only 1 patient, of 86 surviving patients, developed epilepsy after resolved encephalitis. CONCLUSION: Epilepsy after resolved encephalitis was rare in our cohort of patients with AIE treated with immunotherapy. In addition, seizure freedom is achieved faster and more frequently after immunotherapy. Therefore, AEDs should be considered as add-on treatment, and similar to treatment of other encephalitis symptoms, immunotherapy is crucial.

Commentary

Seizures are a prominent and early feature of autoimmune encephalitis, a category of diseases that has tremendously expanded over the last decade. This was recognized in the latest version of the classification of epilepsies of the International League Against Epilepsy (ILAE), which introduced the concept of immune epilepsy, defined as "epilepsy that directly results from an immune disorder in which seizures are a core symptom of the disorder."[1,2] As noted by the ILAE Commission for Classification and Terminology, this etiological subgroup deserves to be individualized given the important implications for treatment with immunotherapies.[3-5] Yet, the optimal regimen of immune therapies and the role of conventional antiseizure medications (ASMs) in autoimmune epilepsies are still unclear.

In this observational cohort study by de Bruijn and colleagues, the authors compared the efficacy and safety of immune therapies and of various ASMs in patients with antibody-positive autoimmune encephalitis. In the database of a national reference center for autoimmune neurological disorders, they identified 153 patients with autoimmune encephalitis who were treated between 1999 and 2017. Of those, 110 patients had seizures and were included. Forty-six had anti-leucine-rich glioma inactivated 1 (LGI1), 43 had anti-N-methyl D-aspartate receptor (NMDAR), and 21 had anti-gamma-aminobutyric acid B receptor ($GABA_BR$) antibody-related encephalitis. As expected from prior studies, patients presented various seizure types, including focal and generalized. Approximately half of the patients with anti-LGI1 encephalitis also had typical faciobrachial dystonic seizures (FBDS). Two-

thirds of patients with anti-$GABA_BR$ encephalitis experienced status epilepticus (SE), which was most often refractory.

A first important lesson of this study is that seizures were the presenting symptoms in more than half of the patients (61% of anti-LGI1, 48% of anti-NMDAR, and 76% of anti-$GABA_BR$) and remained the only or the most prominent clinical feature in a substantial minority of them (22% of anti-LGI1 and 9% of anti-NMDAR). This serves as a reminder that an autoimmune etiology should be considered in patients with new-onset seizures, even when all the other features of the full-blown clinical picture of autoimmune encephalitis are missing.[3]

From a treatment point of view, 91% and 92% of patients received ASMs and immune therapies, respectively. The latency from symptom onset to start of ASMs and start of immune therapy was 3 and 30 days, respectively. Given the observational nature of the study, patients received various immune therapies and ASMs alone or in combination. All but one patient received intravenous (IV) steroids (methylprednisolone), plasma exchange, or IV immunoglobulins (Igs), and 17% received a second-line therapy (cyclophosphamide, rituximab). Two-thirds of patients received 2 or more ASMs. The most commonly used drugs were levetiracetam (66%), valproate (53%), carbamazepine (32%), phenytoin (30%), and clobazam (15%). Lacosamide, oxcarbazepine, lamotrigine, topiramate, and phenobarbital were used in fewer than 10% of patients each, precluding more detailed analysis. When present, cancer was treated.

The second important lesson of the study is that all but one of the 100 patients who received immune therapies and survived became and remained seizure-free. This further underscores the need to identify and adequately treat immune epilepsy, as the prognosis in terms of seizure control is excellent and in fact remarkably higher than the average response of patients with newly diagnosed epilepsy in general. The median time to achieve seizure freedom was 59 days after the start of ASMs and 28 days from the start of immunotherapy, a difference that was highly significant and observed across all 3 syndromes. Importantly, only a small minority of patients achieved seizure freedom while receiving ASMs only. While this study is hampered by all the limitations of its observational design, this finding strongly supports the authors' conclusion that immune therapies are superior to ASMs to achieve seizure control in patients with autoimmune encephalitis. This confirms the results of prior studies in patients with anti-LGI1 and anti-glutamic acid decarboxylase 65 kDa encephalitis.[6,7] As early treatment is associated with better outcome in patients with anti-LGI1 and anti-NMDAR encephalitis[4,5] and seizures occur early in the course of both disorders, especially FBDS in anti-LGI1 encephalitis, it seems appropriate not only to aggressively search for an immune etiology of new-onset epilepsy but also to initiate immune therapies early in the course of the disease. Also, immune therapies will obviously contribute to alleviate the associated nonepileptic manifestations of encephalitis. The study was not designed to compare the different immune therapies and the optimal regimen is still unknown, due to the lack of prospective studies. Most patients were treated according to published guidelines. In short, experts currently recommend to start with first-line drugs (IV steroids + IV Igs), followed by second-line drugs (cyclophosphamide, azathioprine, or rituximab) if the first line is ineffective.

Even if immune therapies are the mainstay of treatment, most patients will still require ASMs to reduce seizure frequency, albeit partially and transiently, especially in case of SE or seizure clusters. Findings from this cohort study, as well as another recent study, tend to suggest that sodium channel blockers, and in particular carbamazepine, might be superior to other medications, such as levetiracetam and valproate, and should be favored. However, these findings should be interpreted with caution. In addition to the uncontrolled open-label design of the study and the heterogeneity of the ASM regimens that were used, variables that may affect the response to treatment, such as indication (discrete seizures vs SE), mode of administration (oral vs IV; use of a loading dose, etc), initial dose, rate of dose increment, if any, maximal dose, and order of use, were not reported. Levetiracetam and valproate are both widely available as IV formulation. They are also recommended as second-line medications for benzodiazepine-resistant SE. It is thus likely that they were favored in more acute situations, as indicated by the fact that no patients with anti-$GABA_BR$ encephalitis, which frequently manifests with SE, including refractory SE, and few patients with anti-NMDAR, which often causes profound encephalopathy, received carbamazepine. This allocation bias will tend to overestimate the efficacy of other medications, such as carbamazepine. Also, as acknowledged by the authors, treatment efficacy was sometimes difficult to assess and was not scored using metrics most epilepsy specialists will be familiar with, such as 50% seizure reduction. Thus, while achieving seizure freedom was likely a robust end point, the distinction between no effect and some effect could have been difficult to make and prone to subjective interpretation. Further, while the authors followed the most recent classification of seizures and epilepsy, the problem of electrographic seizures in encephalopathic patients and their distinction from rhythmic and periodic patterns were not clearly addressed. Patterns such as the extreme delta brush of anti-NMDAR encephalitis are sometimes mistaken for electrographic SE but are unlikely to respond to ASMs. Similarly, it is interesting to note that of all seizure types, FBDS were the least responsive to ASMs. The epileptic nature of these episodes is still debated and some authors consider that they are rather a paroxysmal movement disorder, a condition that is known to respond at least partially to carbamazepine.

In terms of adverse events, they were more frequently reported by patients with anti-LGI1 encephalitis (37%) than by patients with anti-NMDAR (18%) and anti-$GABA_BR$ (15%) encephalitis, who were probably not conscious enough to report them. In addition to a rather high incidence of rash observed with carbamazepine, cognitive and behavioral adverse events were the most frequent, especially with

levetiracetam. The authors did not report the incidence of hyponatremia due to the syndrome of inappropriate secretion of antidiuretic hormone (SIADH). It is both a common adverse effect of carbamazepine, occurring in up to 21% of patients above 40 years of age, and a frequent manifestation of the anti-LGI1 encephalitis, occurring in up to 88% of cases.[8,9] One could wonder if carbamazepine might worsen the SIADH and hyponatremia caused by anti-LGI1 encephalitis. Finally, it should be kept in mind that drug–drug pharmacokinetic interactions can occur between ASMs and immune therapies. For instance, carbamazepine, a moderate cytochrome P oxidase (CYP) 2B6 and a strong CYP3A4 inducer, may influence the levels of cyclophosphamide, a CYP2B6 substrate, and of steroids, which are CYP3A4 substrates. Conversely, plasma exchanges can cause significant decreases in serum levels of ASMs, depending on their distribution volume and protein binding.

Altogether, findings from this study further indicate that we should be prompt to consider an immune etiology in new-onset epilepsy. In addition to early diagnosis, early treatment with immune therapies likely improves outcomes and, with near-complete seizure freedom, appears vastly superior to treatment with ASMs. A temporary course of ASMs is often still required to reduce seizure frequency or treat SE while waiting for immune therapies to exert their full effect, which may take days to weeks. Available evidence is still too scarce and too biased to justify strong recommendations on the choice of ASM. While waiting for more solid evidence, hopefully from a randomized controlled trial, this choice should be made on an individual basis, integrating both clinical and pharmacological considerations.

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