Management of autoimmune encephalitis

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Purpose of review
Autoimmune encephalitides are established diagnoses in contemporary neurology. Their management poses a regular challenge for almost all neurologists. One may ask if the concept of 1st line and 2nd line treatment is still up to date, which new data on the antibody-defined encephalitis types exist, and how to organize long-term management.

Recent findings
The 1st line/2nd line concept of initial immunological intervention is accepted worldwide. A randomized controlled trial confirmed that one 1st line compound (intravenous immunoglobulins) is superior to a placebo in patients with antibodies against leucine-rich glioma inactivated protein 1. Rituximab, a 2nd line compound, is increasingly and apparently successfully used in treating different types of autoimmune encephalitis. It may find its place even earlier in the treatment cascade. Long-term management needs to be improved and is under development.

Summary
There have been no groundbreaking new developments in the field. The published experience confirms existing suggestions. Aspects of long-term management including rehabilitation measures and counseling about driving eligibility require further research.

Keywords
acute symptomatic seizures, autoimmune encephalitis, immunotherapy, rehabilitation, rituximab

INTRODUCTION

For most neurologists, 'management of autoimmune encephalitides' refers to the initial treatment approach, i.e., during the first few months after a diagnosis has been made. Indeed, this is a crucial period with implications for long-term outcome. Its major component is immunotherapy. Dalmau formulated his concept of a 1st line therapy (steroids and/or plasma exchange and/or intravenous immunoglobulins [IVIG]) followed by 2nd line therapy for nonresponders (rituximab and/or cyclophosphamide) in 2011 for anti-N-methyl-D-aspartate receptor (NMDAR) encephalitis [1]. It has readily been adopted for other subgroups of autoimmune encephalitis [2].

The present review tries to answer the following questions: has this concept stood the test of time? Have other medications been suggested beyond those suggested by Dalmau *et al.*? In addition to anti-NMDAR encephalitis, studies on other antibody-associated forms of autoimmune encephalitis are reviewed. Please note that all immunotherapies are off label for the use in autoimmune encephalitides.

In addition to immunotherapy, antiseizure medication (ASM) is given to many patients. Do sodium channel blockers have advantages [3–5]? Finally, long-term management of autoimmune encephalitides is a challenge. How long should patients be kept on the initial therapies?

Pertinent papers were selected from the results of a PubMed search with the string '(autoimmune encephalitis) AND (management or treatment or rehabilitation)' for the period between June 2019 and October 2020, which returned 316 hits.

INITIAL TREATMENT OF AUTOIMMUNE ENCEPHALITIDES

Immunotherapy is the mainstay of treatment for autoimmune encephalitides. ASM are frequently prescribed because most patients have recurrent acute-symptomatic seizures.

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KEY POINTS

- The 1st line/2nd line concept of immunotherapies has been accepted worldwide.
- Seizures have become a useful outcome measure for autoimmune encephalitides.
- Case reports and small series may be valuable, but they can also be misleading.
- Long-term management of patients after the acute stage needs to be improved and refined.

Immunotherapy in general, and outcome comparison of antibody-defined groups

The treatment intensity and outcome of antibody-associated conditions were assessed retrospectively through questionnaires filled in by the treating physicians of patients with the anti-NMDAR neural antibodies leucine-rich glioma inactivated protein 1 (LGI1), contactin-associated protein-2 (CASPR2), and glutamic acid decarboxylase (GAD). There were 251 responses. After an average of two and a half years, patients had received means of 1.5 (GAD antibodies), 2 (LGI1 and CASPR2 antibodies), and 2.8 immunotherapies (NMDAR antibodies). The best outcomes and the largest numbers of improving patients (as measured by a reduction on the modified Rankin scale [mRS] of ≥ 1) were noted in the NMDAR and LGI1 groups (around 80%). In the GAD group, improving and deteriorating patients were similarly frequent (each about 20%), but the majority remained unchanged. CASPR2 patients lay in between, with about 60% of patients showing improvement [6]. These findings confirm previous data that showed NMDAR and LGI1 antibodies to be highly immunotherapy-responsive and GAD antibodies to be poorly responsive. The intermediate position of CASPR2 antibodies was not fully expected, because these were previously thought to go with the very responsive antibodies against surface antigens NMDAR and LGI1.

A multicentric Dutch group provided valuable data on the treatment and outcome of autoimmune encephalitides ($n = 110$) with antibodies against the NMDAR, LGI1, and the γ-aminobutyric acid-B receptor ($GABA_BR$). The authors looked at the symptom 'epileptic seizures' as the primary outcome [7▪▪]. They had already considered the difference between acute symptomatic seizures secondary to autoimmune encephalitis and epilepsy, and their findings were later elaborated by a task force of the International League against Epilepsy [8▪]. The patients in the Dutch report responded better to immunotherapy than to ASM. It took a median of 28 days to seizure-freedom with immunotherapy as compared with 59 days with ASM. Only 1/86 surviving patients were said to have developed epilepsy. Conspicuously, the paper omitted patients with CASPR2 antibodies [7▪▪]. The variable 'seizures' has been used by others, too, to assess the outcome of autoimmune encephalitides. One group identified interictal epileptiform potentials and, more robustly, late onset of immunotherapy (>28 days after symptom onset) as predictors of persisting seizures in cases with NMDAR, LGI1, or $GABA_BR$ antibodies [9].

Suggestions for the formal management of autoimmune encephalitis in general have been provided by an Italian multicenter group [10]. In the immunotherapy section, the authors support the 1st and 2nd line concept [1] for the initial treatment approach. They discuss the value of long-term maintenance therapy and contemplate tentatively the use for at least 1–2 years of azathioprine, mycophenolate mofetil or methotrexate [10].

Three patients with autoimmune encephalitis and antibodies against the NMDAR, LGI, or voltage-gated calcium channels responded favorably to rituximab after corticosteroids had brought about only partial improvement [11]. This type of experience was systematically assessed in a meta-analysis of 2nd line use of rituximab in 277 patients with autoimmune encephalitis (not restricted to certain antibody types) in 14 publications [12]. The authors found good outcomes (mRS ≤ 2) in three-quarters of the patients. The mean reduction of the mRS was 2.7 (95% confidence interval: 2.1–3.3). The benefits seemed particularly obvious in patients with anti-NMDAR encephalitis. Treatment success was inversely correlated with disease duration at the start of rituximab administration – which might be an argument for earlier use of this compound. Sixteen percent of patients for whom data on side effects was available ($n = 184$) had infusion reactions; 6% acquired pneumonia and 1% septicemia. This was in accordance with previous observations of neurological conditions. Over an average follow-up of 1 1/4 years, no renal, blood, or lymphatic system-related adverse events were reported. The authors concluded that rituximab is a viable 2nd line option, perhaps to be used earlier than previously. This suggestion is in keeping with the results of a recent worldwide survey on treatment habits in autoimmune encephalitides, wherein it was found that neuroimmunology experts take a more 'proactive' therapeutic approach—including early escalation strategies—than other neurologists [13].

Anti-N-methyl-D-aspartate receptor encephalitis

This prototype of autoimmune encephalitis still inspires most publications in this field. Josep

Dalmau *et al.* have published a major update on the condition. The authors renewed their previous endorsement of the 1st and 2nd line therapy concept and criticized the interpretation of some recent case report-based treatment considerations [14▪]. Another group looked for factors affecting the response to 1st line therapy (steroids plus IVIG) in 29 of their own patients. The authors found signs of more severe disease to be predictive for the need for 2nd line therapy [15]. Similarly, a recent case series from Pakistan ($n = 8$) reproduced the management experience of a classical series on this condition. It suggested that a better outcome might be possible if steroid therapy was offered in combination with another immunological agent [16]. One severely affected young woman recovered with multidisciplinary intensive-care management and with escalating immunotherapy, again including rituximab as 2nd line treatment [17].

A couple of years ago, a number of case reports and small series suggested the use of the proteasome inhibitor bortezomib (aimed at antibody-producing plasma cells) or the monoclonal antibody tocilizumab (an interleukin-6 blocker) as 3rd line therapies in anti-NMDAR encephalitides. Both compounds have been described as useful in recent case studies [18–20].

Anti-leucine-rich glioma inactivated protein 1 encephalitis

The Mayo Clinic group reported the first randomized controlled treatment trial in patients with autoimmune encephalitides [21▪▪]. The authors intended to randomize 30 patients with LGI1 or CASPR2 antibodies to IVIG, and 30 patients to a placebo. For a schematic representation of the protocol, see Fig. 1. Even though the authors identified 594 patients with the target antibodies through their laboratory service over 3 years, only 17 patients could be randomized (8 to IVIG, all with LGI1 antibodies; 11 to placebo: LGI1, $n = 6$; CASPR2, $n = 3$). Even with this reduced sample size, IVIG-treated patients more often achieved a $\geq$50% reduction in seizure frequency (the primary outcome variable). The placebo patients experienced the same effect in the open extension.

Anti-contactin-associated protein-2 encephalitis

One such patient improved after five months of unsuccessful immunotherapy trials upon administration of 13 cycles of 16 mg/kg of the anti-CD38 antibody daratumumab [22]. The rationale of this intervention was the same with bortezomib: the compound reduces the number of antibody-producing plasma cells.

Anti-neurexin-3α encephalitis

Like CASPR2, neurexin-3α is a cell surface molecule that acts as an adhesion molecule between presynapses and postsynapses. Antibodies against this antigen have been described in patients with autoimmune encephalitides quite similar to those in anti-NMDAR encephalitis but with a poor prognosis. One case responded fully to rituximab therapy after the failure of methylprednisolone and plasma exchange [23].

Glutamic acid decarboxylase antibody-associated limbic encephalitis

GAD antibodies differ from those discussed above. They are directed against an intracellular target and are almost certainly not directly pathogenic. Patients respond poorly to immunotherapy. Only a minority of cases develops a limbic encephalitis meriting the diagnosis of 'definitive autoimmune

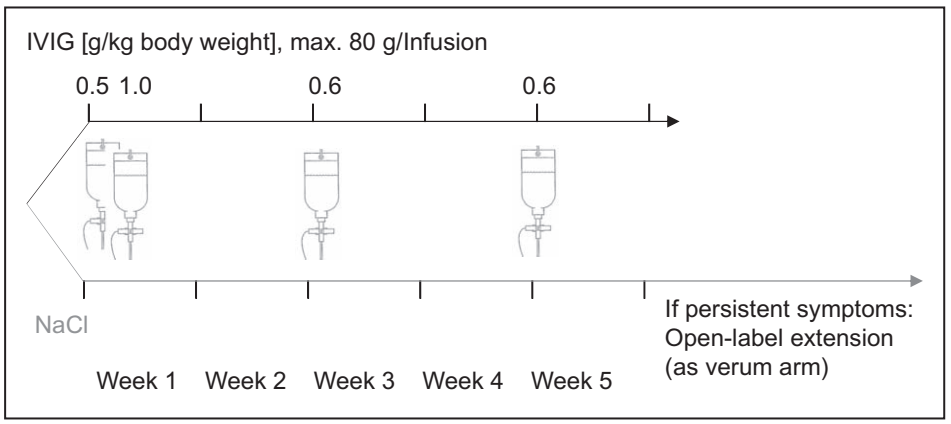

FIGURE 1. Schematic representation of the treatment protocol of the randomized controlled trial in patients with LGI1 or CASPR2 antibodies [21▪▪]. CASPR2, contactin-associated protein-2; LGI1, leucine-rich glioma inactivated protein 1.

encephalitis;' most take a chronic disease course. A recent major review article summarizes in a masterly way the existing knowledge on GAD antibodies in neurological diseases [24▪▪].

One middle-aged woman with GAD antibodies (a typical patient [6]) developed limbic encephalitis. She was diagnosed and treated with five infusions of 1 g methylprednisolone 1 month after the manifestation of the disease. Her symptoms remitted quickly [25]. A similar case with treatment started after six weeks and the rapid and complete recovery has been included in a larger series [26▪].

IgLON family member 5 antibody-associated disease

IgLON family member 5 (IgLON5) is also an intracellular antigen. Antibodies against IgLON5 were initially reported to indicate immunotherapy-resistant conditions with features of autoimmunity and neurodegeneration. A systematic meta-analysis revealed that a prolonged reduction on at least one symptom of anti-IgLON5 disease could be achieved in one-third of treated cases, especially alongside 1st line therapies with azathioprine or mycophenolate mofetil [27].

Paraneoplastic encephalitides with >1 antibody

A 65-year-old woman with a history of breast cancer presented with a tonic-clonic seizure, involuntary movements (tremor or myoclonus) and depression. She harbored antibodies against dipeptidyl-peptidase-like protein-6 and aquaporin 4. She had no tumor relapse, but despite prednisolone and azathioprine therapy, she had a relapsing course with cognitive deterioration [28]. A combination of $GABA_BR$ and Sox1 antibodies occurred in a 59-year-old female patient with memory loss, computational difficulties, and seizures. This constellation was correctly interpreted as indicative of a paraneoplastic encephalitis. This led to the detection of a small cell lung cancer. The patient was said to have improved neurologically upon administration of a single five-day-course of IVIG plus the institution of levetiracetam [29].

Antiseizure medication

The effect of ASM on acute symptomatic seizures in autoimmune encephalitides is probably marginal. Nevertheless, 91% of patients with seizures in one study received ASM [7▪▪]. The previous observation that sodium channel blockers are more effective than others (including levetiracetam) was not confirmed in a recent Dutch series. The authors showed the effect of valproic acid, levetiracetam, and carbamazepine. In anti-LGI1 encephalitides, carbamazepine appeared more effective than the other two compounds, but at the price of more frequent skin rashes. There was no difference in efficacy in patients with NMDAR or $GABA_BR$ antibodies [7▪▪].

LONG-TERM MANAGEMENT

In clinical reality, matters do not come to an end after 1st line and perhaps 2nd line immunotherapy, with or without an ASM. Whether a 3rd line therapy should be administered to patients who do not respond satisfactorily is just one issue. Well-responding patients, too, raise the question of how long the initial therapy should be administered. There is a broad spectrum of treatment habits among neurologists. The Netherlands multicenter study illustrated this clearly. The authors reported that ASM was given for a median period of eight months after diagnosis, with a large range of 0–102 months [7▪▪]. The reason for the spread was a lack of suggestions concerning the discontinuation of the therapy. This is related to uncertainties about reliable prognostic parameters, as discussed in the review article on anti-NMDAR encephalitis. Its authors repeated the notion that one should rely on the clinical picture more than on any test when making treatment decisions [14▪]. Long-term immunotherapy using compounds such as azathioprine or mycophenolate mofetil is still conducted on the basis of individual decision making rather than solid evidence [10]. The Dutch study found lower relapse rates in patients receiving such treatment, but the difference was not statistically significant [7▪▪].

The long-term cognitive sequelae of autoimmune encephalitides can be severe. With immunotherapy, most patients improve dramatically from their disease nadir, but they are often left with a cognitive and behavioral performance below their premorbid level. In one study, most individuals with anti-NMDAR encephalitis ($n = 61$) had a mRS ≤ 2, which indicates a good neurological outcome. However, they had a lower psychosocial function after a mean of 4.4 years (with a range of 0.6–13.3 years) after symptom onset compared with a normative sample of patients with chronic diseases. Return to work or school was negatively correlated with an initial misdiagnosis (and probably protracted immunotherapy) and was positively correlated with a follow-up with a psychiatrist after hospitalization [30].

In view of these issues, rehabilitation treatment for patients after autoimmune encephalitis may be important. Suggestions for an individual approach to such patients have been provided [31]. Beyond cognitive training and psychiatric stabilization,

assessment of social restrictions such as driving capacity is also important. This cannot be carried out simply along the lines of the epilepsy rules because autoimmune encephalitis produces acute symptomatic seizures, not epilepsy [8▪]. There are, however, usually no regulations in the guidelines on driving capacity for people who experience repeated acute symptomatic seizures. An exception is the United Kingdom, which allows an individual to drive six months after their last seizure secondary to limbic encephalitides [32]. Data on the risk of seizure relapse have been reviewed. The authors suggest tentatively that six, perhaps even only three months of seizure freedom after the last seizure secondary to autoimmune encephalitis might be sufficient to predict a relapse risk $< 20\%$ in the following year. This would satisfy European driving regulations [33].

CONCLUSION

In the last 18 months, few exciting original studies on the management of autoimmune encephalitis have appeared. The papers reviewed, however, permit some conclusions to be made and some trends to be highlighted. The concept of 1st line therapy (steroids, IVIG, plasmapheresis) and 2nd line therapy (rituximab and/or cyclophosphamide) [1] has been accepted by the community worldwide. A randomized controlled trial has confirmed the superiority of a single 1st line intervention (IVIG) over a placebo in encephalitides with LGI1 (or CASPR2) antibodies [21▪▪]. Rituximab is appearing more frequently in the literature on a range of conditions involving neural antibodies. Overall, the results are positive. Rituximab also shows the potential to be introduced at an earlier stage. Cyclophosphamide is less frequently mentioned. The potential of a 3rd line therapy (mainly in anti-NMDAR encephalitis) is currently being debated. Based on existing reports, it is impossible to say how much a 3rd line compound might contribute immediately after the administration of a 1st and 2nd line compound [14▪]. Fortunately, a prospective randomized controlled trial with bortezomib has just begun [34].

Outcome assessment has largely relied on the—rather coarse and sometimes subjective—mRS. Recently, seizure counts or seizure freedom have become additional outcome criteria. They offer the advantage of metric or categorical data [7▪▪,9,21▪▪]. A problem with two studies that used seizures as an outcome parameter [7▪▪,9] was that 'epilepsy' after autoimmune encephalitis [8▪] was not clearly differentiated from the preceding period of acute symptomatic seizures. It must be noted, however, that suggestions on how to define when a patient begins to have epilepsy are only tentative [26▪,35].

It seems that there are almost no new data on CASPR2 antibodies, even though these were among the four most frequent relevant neural antibodies in a 2020 study [6]. CASPR2-abs were not included in two larger recent studies [7▪▪,9]. This may be because the outcomes were less favorable than would previously have been envisaged and that the clinical phenotype and the demographic range is expanding, potentially raising concerns of antibody specificity [36].

The above literature survey shows that case reports in small series may be beneficial in highlighting instructive, exotic, or otherwise meaningful, special, and rare constellations [25,28,29]. There are, however, problems with case reports that focus on successful novel treatments. Such papers may report positive examples and ignore less favorable ones (publication bias); high expectations resulting from plausible mechanisms of action may give rise to placebo effects or overoptimistic outcome evaluations. In the absence of control patients, spontaneous recoveries or the delayed effects of previous treatments may be mistaken as the outcome of recent interventions. Once such papers become part of meta-analyses, these effects may even be inflated.

ASM offers an example of symptomatic add-on therapy, and it is part of the treatment reality. Existing data permit at least an estimate of its efficacy and tolerability [7▪▪].

Long-term management [30] is also important, but it requires further development. It is pleasing to note that postacute interventions to improve the behavioral, cognitive, and social outcome are being implemented [31]. One aspect of such rehabilitative efforts is an adequate assessment of fitness to drive among patients after repeated acute-symptomatic seizures [37]. Here, the database will need to be expanded before more concrete recommendations can be made.

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