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PRELIMINARY REPORT

Efficacy of add-on Cenobamate treatment in refractory epilepsy due to Rasmussen's encephalitis

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Abstract

Objective: To assess antiseizure effects of cenobamate, a new antiseizure medication with at least two mechanisms of action, in the rare, highly pharmacoresistant and progressive epilepsy syndrome related to Rasmussen's encephalitis.

Methods: Three patients from the epilepsy centers in Freiburg, Kork, and Valencia are reported with focal epilepsy which had been pharmacoresistant to more than 10 prior treatment regimens. Assessment included at least 1 year of follow-up after cenobamate introduction and included seizure frequency, seizure severity (in particular status epilepticus) and changes in co-medication.

Results: In the three patients, cenobamate add on treatment proved superior to all prior antiseizure and immunomodulatory treatments which had been individually applied. Not only were focal to bilateral tonic–clonic seizure completely controlled, but also focal motor status epilepticus no longer occurred. Co-medication could be reduced in all patients.

Significance: This case series in a rare and highly pharmacoresistant epilepsy syndrome suggests high efficacy of cenobamate add-on treatment for seizure control. This may be a valuable information in epilepsy related to Rasmussen encephalitis and calls for further elucidation of the mechanism involved in superior seizure control also compared to prior treatments including sodium channel blockers and benzodiazepines.

Plain Language Summary: Rasmussen's encephalitis is a rare type of epilepsy that gets worse over time and doesn't respond well to most seizure medications. We describe three patients who tried many treatments without much success, but when they added cenobamate to their treatment, it worked better than the other medications. This also let them lower the overall amount of medication they were taking.

KEYWORDS

cenobamate, epilepsy, pharmacotherapy, Rasmussen's encephalitis

1 | INTRODUCTION

Rasmussen's encephalitis is a rare disease with an estimated incidence of 1.7–2.4/10 million people[1,2] and a prevalence of 0.18 per 100.000 people. It is characterized by progressive unilateral hemispheric atrophy, pharmacoresistant focal epilepsy, contralateral hemiparesis, and potential cognitive decline. Epilepsy starts during childhood or early adulthood (median age at onset: 6 years).[3,4] More than half of the affected patients develop status of focal clonic seizures (epilepsia partialis continua, EPC[5]). There is an underlying unilateral encephalitis with an early involvement of the periinsular regions of so far unknown origin, assumedly due to an autoimmune process. Histological investigations suggest a key role of cytotoxic T-lymphocytes and microglia, as well as of autoantibodies as part of the inflammatory process.[6]

Rasmussen's encephalitis is considered pharmacoresistant to all available antiseizure medications (ASMs),[7] and treatment mostly aims at controlling the progression of focal to bilateral tonic–clonic seizures.

Hemispherotomy is considered the by far most efficacious treatment option and only cure, yet implies resulting motor and possibly cognitive defects, which particularly matter if the progressive encephalitis is lateralized to the dominant hemisphere. Immunological treatment has been attempted with a wide spectrum of agents, including long-term or pulsed corticosteroids, intravenous immunoglobulins, plasmapheresis, immunoabsorption, azathioprine, tacrolimus and T-cell directed monocloncal antibodies, with so far unclear preference, yet at times controlling disease progression.[7]

So far, there are no data showing the superiority of any specific ASMs to better control seizures in Rasmussen's encephalitis. Here we report three encouraging cases of people with highly pharmacoresistant epilepsy due to Rasmussen's encephalitis in whom the introduction of cenobamate led to major improvements of seizure control over a period of more than a year at last follow-up.

Key points

- Cenobamate add-on treatment showed efficacy superior to previous treatment approaches in three patients with epilepsy due to Rasmussen's Encephalitis.
- Efficacy of cenobamate was particularly pronounced with regard to prevention of status epilepticus and focal to bilateral tonic–clonic seizures.
- Cenobamate was also effective in patients who had less well controlled seizures with a combination of other sodium channel blockers and benzodiazepines.
- Cenobamate add-on treatment allowed to reduce the total drug load.

2 | CASE REPORTS

2.1 | Case 1

A 32-year-old male patient had no risk factors for epilepsy when seizures started at the age of 10 years. Seizures were focal aware motor with rhythmic clonic movements of his right arm and face which could show Jacksonian march to the right leg, and were at times associated with aphasia (difficulties in word finding and speech arrest). Seizures could progress to focal unaware seizures with areagibility, or to nocturnal tonic–clonic seizures. Prolonged focal aware clonic motor seizures already occurred for hours as focal status epilepticus (Epilepsia partialis continua, EPC) early after onset of epilepsy.

EEG showed left fronto-temporal slowing and left frontal interictal spiking, ictal recordings confirmed a frontal seizure onset (Figure 1A and 1B). MR imaging of the brain showed left fronto-insular hyperintensity and periinsular atrophy (Figure 2).

Histological findings from an open biopsy performed at the age of 10 years showed signs of a florid encephalitis with perivascular and intraparenchymal CD-8 positive T-cells and Granzyme B-positive cytotoxic T-cells in close apposition to neurons as well as activated microglia, thus expressing typical features of a Rasmussen-Encephalitis.

From 2009 to 2021, this patient received treatment with a total of 10 ASMs (phenytoin max. 500 mg/day, valproate max. 4000 mg/day, levetiracetam max. 2000 mg/day, oxcarbazepine max. 1800 mg/day, lamotrigine max. 200 mg/day, lacosamide max. 375 mg/day, clobazam max. 30 mg/day, cannabis-inhalation, perampanel max. 14 mg/day, brivaracetam max. 200 mg/day), mostly prescribed in polytherapy consisting of 2–4 ASM and at dosages approaching impaired tolerability, including ataxia with phenytoin and lacosamide, hyperammonemia with valproate, and sedation with clobazam and perampanel.

Treatment efficacy was fluctuating with periods of weeks to months without seizures yet regular recurrence and periods of status epilepticus requiring ICU treatment. For several years, recurrences of severe and frequent seizures corresponded to phenytoin serum levels; any attempts to withdraw phenytoin failed, and complete seizure control was never achieved for more than 3 months. The patient developed an overlasting Todd's paresis which

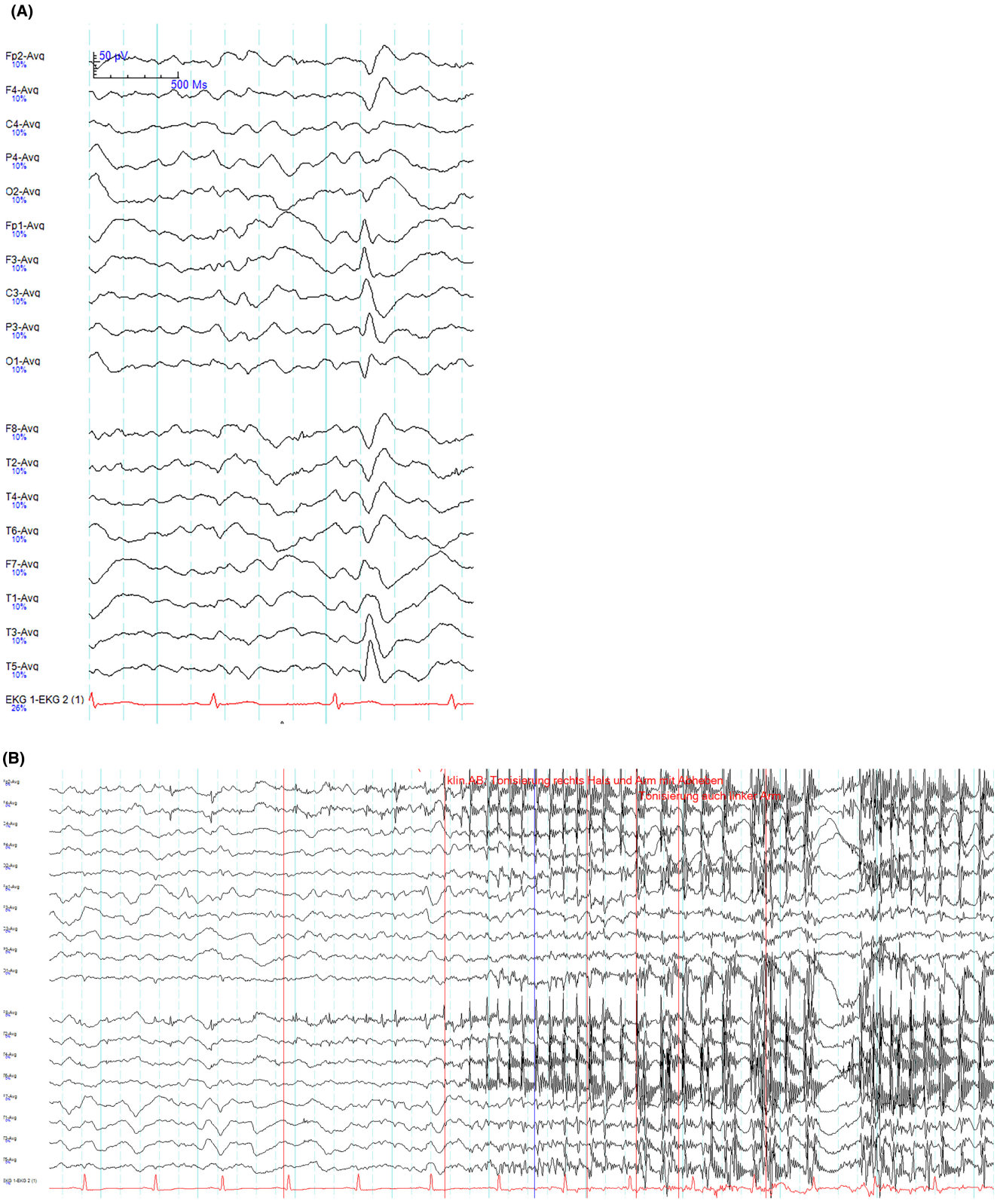

FIGURE 1 Left fronto-temporal Interictal spiking (A) and seizure onset (B) note right-sided rhythmic muscle artifacts during the unilateral focal clonic seizure.

only transiently improved with Lorazepam application, became wheelchair-bound and dependent on the care of his family.

Presurgical monitoring was performed, but he was not considered a surgical candidate due to left-sided MR atrophy, ictal aphasia, onset of seizures only at age 10, and

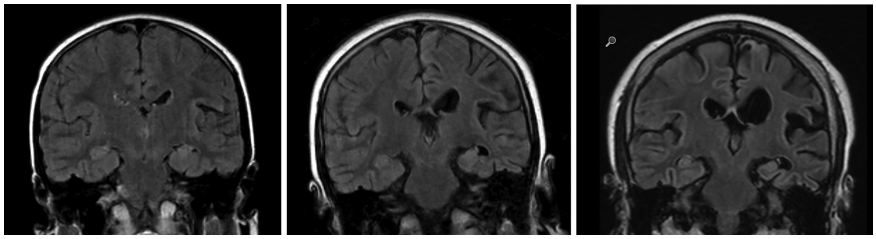

FIGURE 2 Progressive left perisylvian atrophy during early years of the disease (2001, 2003, 2009), with more stable findings thereafter.

complete ictal aphasia during a left-sided intracarotid amytal (Wada) test, prohibiting a left sided hemispherotomy.

Additional immunomodulatory treatments were performed consecutively over many years and consisted of corticosteroids (prednisone), azathioprine, methotrexate, mycophenolate-mofetil and i.v. IgG, with limited or transient efficacy on seizure frequency and severity; corticosteroid treatment induced both, obesity and steroid myopathy. Lately, in 2018, adalimumab was applied which resulted in transient major seizure reduction yet adverse effects and seizure recurrence with focal status epilepticus and was thus discontinued in 2020.

In 2021, Cenobamate was introduced add-on to a baseline medication of valproate 3000 mg/day and phenytoin 300 mg/day. Already at a dosage of 100 mg CNB/day this resulted in complete seizure control for a period of 1 year. Given this extraordinary efficacy, valproate was completely tapered off without seizure recurrence, and the phenytoin dosage could be reduced from 300 to 150 mg/day with parallel increase in CNB dosage to 200 mg/day. During a consecutive complete discontinuation of phenytoin, some focal aware motor seizures reoccurred which have so far been so mild that no adaptations of medication were requested by the family.

2.2 | Case 2

A presently 28-year-old male patient had an onset of seizures at the age of 5 years and 11 months. Semiologically, seizures types were focal aware sensory seizures with an epigastric sensation, focal unaware motor seizures with clonic movements of the right side, oral automatisms with and without hyperkinetic movemenets of the right side and focal to bilateral tonic–clonic seizures.

Over the course of time, the patient developed a gradually increasing spastic right sided hemiparesis. EEG showed a continuous slowing over the left hemisphere and left centro-temporal and at times left occipital sharp waves. Ictal EEG showed left hemispheric rhythmic theta activity.

MRI showed a progressive hemispheric atrophy which remained stable in adulthood. A stereotactic biopsy confirmed a suspected Rasmussen's encephalitis. In a Wada test performed at the age of 8 years, left intracarotid amytal injection resulted in a complete aphasia, whereas Doppler tests showed bilateral perfusion increases of the ACM during language activation. At this time, the patient was not considered a surgical candidate due to a high risk of loss language capabilities.

Antiseizure treatment was performed with phenobarbitone, valproate, carbamazepine, phenytoin, topiramate, levetiracetam, zonisamide, lamotrigine, lacosamide and oxcarbazepine in mono- or combination therapy with often three ASM, yet without satisfactory seizure control. Adverse treatment-related effects included sedation, blurred vision, diplopia, ataxia, dysarthria and a pancreatitis under high-dose valproate therapy. Attempts to reduce high-dose phenobarbitone with serum levels around 70 μmol/mL failed due to massive seizure aggravation.

Also, an immunomodulatory therapy with tacrolimus did not improve the clinical situation.[8] Language capabilities gradually decreased over time, yet the option of a left-sided hemispherotomy was not agreed upon by his parents.

By the end of 2020, cenobamate was given add-on to a baseline medication of 225 mg PB and 1200 mg oxcarbazepine/day. With CNB uptitration to 200 mg/day, sedation resulted with increased levels of PB. Tolerability was improved when reducing PB to 200 mg daily. Seizure frequency immediately fell from daily seizures to about 10/month, i.e., by more than 50%, and there was no more progression from focal to bilateral tonic–clonic seizures after a treatment period of 11 months. Further increase of CNB to 300 mg/day again induced sedation, and parents insisted on CNB reduction back to 200 mg/day. Phenobarbitone could be reduced to 75 mg/day without deterioration.

A second attempt to increase the CNB dosage from 200 to 300 mg/day did not result in additional benefit. The patient has now been on a stable and well-tolerated regime with CNB 200 mg/day, PB 100 mg/day, and OXC 1200 mg/day, with respective serum levels of 21.8, 44.7 and 22.3 μg/mL, and has been a stable responder with a seizure reduction by >50% and complete control of focal to bilateral tonic–clonic seizures for more than 2 years.

2.3 | Case 3

This patient is a 42-year-old right-handed male without risk factors for epilepsy. Seizures started at the age of 16

and consisted of right homonymous hemianopsia, and flashes of lights without other semiology lasting 2–3 min. Initially diagnosed with visual auras without migraine, it was not until he had his first bilateral tonic–clonic seizure at the age of 22 when the diagnosis of epilepsy was established. Complete seizure control was achieved with valproate and topiramate until the age of 33, when other stereotyped seizures began, characterized by paraesthesias over the right arm (sometimes preceded by visual impairment) for 2–4 min, and episodes of staring and loss of awareness followed by post-ictal amnesia and language impairment (sometimes preceded by sensitive and/or visual symptoms). The average frequency of these seizures was 5–10 per month, so after trying oxcarbazepine and levetiracetam, the patient was referred for presurgical evaluation when he was 35 years old. Video-EEG monitoring registered left posterior quadrant slowing and epileptiform discharges as well as seizures with onset over this region with left temporal and left parietal spreading patterns. A 3 T brain MRI with a specific epilepsy protocol and positron emission tomography (FDG-PET) revealed slight atrophy and extensive hypometabolism over the left parieto-occipital cortex, so type I cortical dysplasia was suspected (Figure 3). Due to the risk of post-surgical deficit, surgery was ruled out.

Over the next 5 years, the frequency of the seizures was variable, ranging from several focal without awareness impairment per day and 2–3 impaired-awareness seizures per week to 1–2 weeks without seizures, despite different treatment adjustments with perampanel, brivaracetam, zonisamide, lacosamide, and carbamazepine. At the age of 39, the patient began to associate another type of seizures characterized by paraesthesias over the right arm followed by hypersalivation, dysarthric speech and right face and arm twitching without impaired awareness. Clobazam at a dose of 30 mg per day was added to levetiracetam (3000 mg/day), lacosamide (400 mg/day), and carbamazepine (600 mg/day), with a 25% decrease in all types of seizures. However, motor twitching in the right arm became essentially continuous during both wakefulness and sleep, evolving into epilepsia partialis continua (EPC) with slight right hemiparesis, choreodystonic posture, and cognitive deterioration. Eight months later, cenobamate was started with the usual dose escalation schedule, up to 200 mg per day, achieving impaired-awareness seizures freedom with an 80% reduction in focal without awareness impairment seizures and arm twitching improvement during 20 months of follow-up. Carbamazepine was progressively withdrawn without worsening.

A new evaluation was carried out with a 3 T brain MRI, revealing generalized involutional changes with prominence of sulci, an increase in extracerebral space, ventricular enlargement, and greater left occipitoparietal involution. Basal ganglia involvement was not observed (Figure 4 and Table 1). Video-EEG monitoring recorded left posterior quadrant slowing and pseudorhythmic and repetitive spikes, independently located over both the left posterior quadrant and the left central and parietal region.

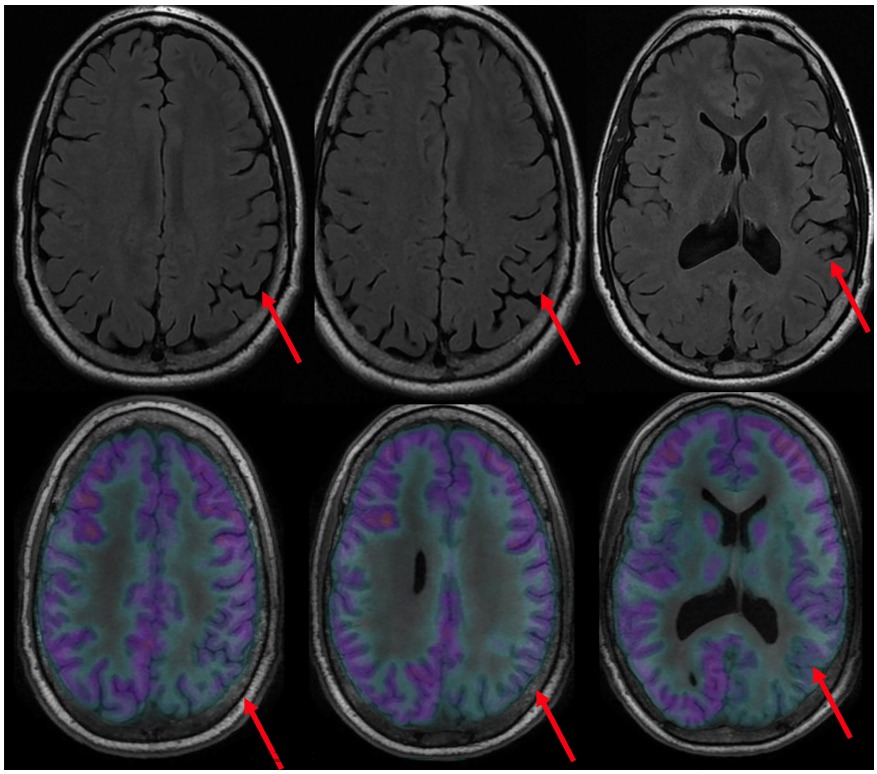

FIGURE 3 Axial fluid-attenuated inversion recovery (FLAIR) (top) and positron emission tomography (FDG-PET) (bottom) showing slight atrophy and extensive hypometabolism over the left parieto-occipital cortex.

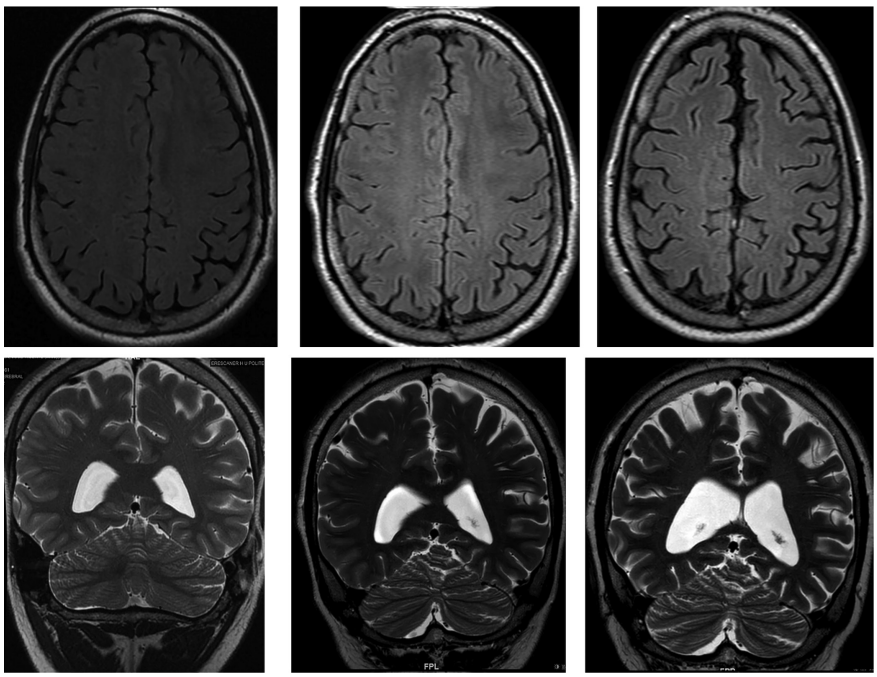

FIGURE 4 Axial fluid-attenuated inversion recovery (FLAIR) (top) and coronal T2 (bottom) images showing progressive generalized atrophy, mainly of the left occipitoparietal region.

Cerebrospinal fluid (CSF) analysis showed the presence of IgG oligoclonal bands. Extensive serum and CSF studies, particularly paraneoplastic and autoimmune encephalitis antibody testing, returned negative results. A neuropsychological study revealed significant dysfunction in attention and executive functions. Genetic testing is pending, and brain biopsy have not yet been performed.

This case does not completely fulfill Bien's criteria for Rasmussen's encephalitis, yet certainly falls into the spectrum of its late-onset form, including slower progression, myoclonic features, EPC and occipital seizure onset.[9–13] Under the suspicion of adult-onset hemispheric encephalitis, with a possible associated focal cortical dysplasia,[14–18] first-line immunotherapy has been recently started.

3 | DISCUSSION

These three cases provide casuistic evidence for an intraindividual superiority of CNB in patients with Rasmussen's encephalitis and a similar case with unilateral progressive hemispheric atrophy compared to >10 previous ASM treatments using drugs with differing mechanisms of actions not only in monotherapy but also in polytherapy (Table 1). Marked antiseizure effects were already present at dosages of 100–200 mg/day.[19] Not only was cenobamate effective, but its introduction also for the first time allowed to reduce comedications which had been indispensable before, e.g., phenytoin in case 1, phenobarbitone in case 2, and carbamazepine in case 3; this is very much in line with a recent analysis by Becker et al.[20] performed in the treatment of focal epilepsy in general.

So far there is no established best medical treatment for Rasmussen's encephalitis. Whereas hemispherotomy is a successful surgical approach,[21] it is invariably associated with a resulting contralateral hemiparesis, and in the three cases with involvement of the left hemisphere, surgery in the language-dominant hemisphere was not an option due to a high risk of resulting aphasia.

Overall, the efficacy of standard ASMs in autoimmune epilepsy is considered very low, with seizure control in about 10% of patients,[22,23] and the number of patients reported as seizure free is too low to draw valid conclusions with regard to optimal mechanisms of action. At least casuistically, the introduction of sodium channel blockers was reported to be more successful than the application of levetiracetam.

In Rasmussen's encephalitis, few case series report effects of individual ASMs; in one publication, one of three patients had some response to clobazam.[24] Some beneficial effects of ASM treatment have been reported for cannabidiol[25] and of vagus nerve stimulation.[26] The casuistic evidence provided here suggests that cenobamate may be considered also as an early add-on treatment in Rasmussen's encephalitis when pharmacoresistance starts to manifest.

Immunotherapy is frequently applied in addition to ASMs; despite a wide spectrum of approaches which have been used (corticosterioids, IV IgG, plasmapheresis, azathioprine, tacrolimus and monoclonal antibodies like rituximab), antiseizure effects of these approaches have remained controversial, whereas some efficacy in slowing cortical atrophy has been reported. In our series, only for rituximab a positive effect was observed on seizure frequency

TABLE 1 Patient characetistics.

	Pat 1	Pat 2	Pat 3
Sex	M	M	M
Age at epilepsy onset	10	5	16
Age at CNB introduction	32	25	40
Imaging	L fronto-insular hyperintensity & periinsular atrophy	L hemispheric atrophy	Slight left parieto-occipital atrophy
Motor function	R-sided spastic paresis, can use a pencil. Wheelchair bound	R-sided spastic paresis, almost complete sensory and motor aphasia	Slight hemiparesis with choreodystonic posture
Cognition	Cognitive slowing, deficits in expressive language, verbal fluency, action planning, attention and memory	Severe cognitive impairment, almost no communication possible	Significant dysfunction in attention and executive functions
Seizure types	Focal aware motor (clonic; EPC) >aphasic Focal unaware Focal to bilateral tonic–clonic	Focal aware sensory, Focal unaware motor/ with automatisms, Focal to bilateral tonic–clonic	Focal aware (visual and sensory) Focal aware (motor with hypersalivation and dysarthria, EPC) Focal unaware Focal to bilateral tonic–clonic
# previously used ASM	10 (BRV, CLB, DPH, LCM, LEV, LTG, OXC, PER, THC, VPA)	10 (PB, VPA, CBZ, DPH, TPM, LEV, ZNS, LTG, LCM, OXC)	10 (VPA, TPM, OXC, LEV, PER, BRV, ZNS, LCM, CBZ, CLB)
Previous antiinflammatory treatments	Prednisone, Azathioprine, Methotrexate, Myceonlate-mofetil Iv IgG, Adalimumab	 Tacrolimus	–
Baseline co-medication	VPA 1000 mg/day DPH 300 mg/day	OXC 1200 mg/day PB 225 mg/day	CLB (30 mg/day) LEV (3000 mg/day) LCM (400 mg/day) CBZ (600 mg/day)
Treatment response	>90% seizure reduction, no more status	>50% seizure reduction, no focal to bilateral tonic–clonic seizures	Focal unaware seizure freedom, 80% focal aware seizure reduction and EPC improvement
Onset of CNB efficacy	100 mg/day	100 mg/day	200 mg/day
Follow-up duration	2 years	3 years	2 years
Final ASM combination	CNB 200 mg/day DPH 150 mg/day	CNB 200 mg/day OXC 1200 mg/day PB 100 mg/day	CNB (200 mg/day) CLB (20 mg/day) LEV (3000 mg/day) LCM (400 mg/day)

Abbreviation: EPC, Epilepsia partialis continua.

in case 1; however, treatment was discontinued due to tolerability problems along with incomplete seizure control.

Cenobamate is considered to exert two main synaptic effects: enhancement particularly of inactivation of (presynaptic) sodium channels, leading to reduced persistent Na-influx and reduced neurotransmitter in a use-dependent way, and positive allosteric modulation of $GABA_A$ receptor-mediated ion channels at a non-benzodiazepine binding site, inducing to postsynaptic inhibition.[27] Already in mixed populations of focal epilepsies, cenobamate has shown excellent efficacy.[28–30] One may thus discuss that these two mechanisms of action, which have been reported casuistically as effects in autoimmune encephalitis, may explain the observed superior efficacy of CNB compared to many pre-treatments. Patient 1 in which CNB efficacy was particularly striking,

had had combinations of several sodium channel blockers with clobazame to maximally tolerated dosages before without a similar efficacy questioning that just combining these MOA fully explains the observed superior efficacy. An anti-inflammatory effect of Na-channel blockers has been discussed based on the role of Na^+ currents on lymphocytes, macrophages and microglia.[31]

The effect of CNB in other forms of autoimmune encephalitis has also been raised by a recent publication on the treatment of GAD-65 positive patients.[32] Here, a high efficacy of CNB with its known dual mechanisms of action was particularly found in combination with clobazam. Notably, cenobamate was effective in two of three cases of Rasmussen's encephalitis reported here in the absence of this combination, which argues for an efficacy of Cenobamate itself rather than possible contributing effects of the known pharmacokinetic interaction causing increases in the active metabolite N-Desmethyl-Clobazam by CYP2C19 inhibition.[33] Further studies are needed to investigate if additional factors contribute to the observed clear CNB superiority to more than 10 pretreatments in the patients with Rasmussen's encephalitis reported here, if this is a general property for the treatment of epilepsy syndromes related to autoimmune encephalitis, and if this renders CNB an additional quality of an orphan drug related to this specific efficacy beyond its general characteristics as a powerful drug in focal epilepsy.[34,35]

AUTHOR CONTRIBUTIONS

ASB, BJS, MH, MG and VV have provided and written details of the case reports. ASB has designed the publication, and BJS and VV have contributed to the discussion.

CONFLICT OF INTEREST STATEMENT

A. Schulze-Bonhage has received honoraria for lectures or advice from Angelini, BIAL, Desitin, EISAI, JAZZ pharma, Precisis, UCB and UNEEG. He has received research support from BIAL, Precisis and UNEEG. B.J. Steinhoff has received advisory and consulting honoraria from Angelini, Jazz/GW Pharmaceuticals, Precisis, Roche Diagnostics, UCB. BJS has received speaker's honoraria from Al Jazeera, Angelini, Bial, Desitin, Eisai, Jazz/GW Pharmaceuticals, Medscape, Tabuk, Teva, UCB, Zogenix. BJS has received research support from the Eisai, the European Union, Jannsen-Cilag, Jazz/GW Pharmaceuticals, SK Life Sciences, UCB, Zogenix. M. Garces has received speaker honoraria from Angelini-Pharma, Jazz Pharmaceuticals, Eisai and Neuraxpharm. M. Hirsch has received lecture fees and consulting fees from the UCB, Eisai, and Angelini Pharma outside of the present work. V. Villanueva has received honoraria and/or research funds from Angelini Pharma, Bial, Eisai, Jazz Pharmaceuticals, Neuraxpharm, Novartis, Nutricia, Paladin, Takeda, UCB Pharma, and Xenon. We confirm that we have read the Journal's position on issues involved in ethical publication and affirm that this report is consistent with those guidelines.

DATA AVAILABILITY STATEMENT

Individual patient data are not available for direct access due to data protection rules.

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