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Research Submission

New-Onset Headache in Patients With Autoimmune Encephalitis Is Associated With anti-NMDA-Receptor Antibodies

Christoph J. Schankin, MD; Fabian Kästele, MD; Lisa Ann Gerdes, MD; Tobias Winkler, MD; Endy Csanadi, MD; Tobias Högen, MD; Hannah Pellkofer, MD; Walter Paulus, MD, PhD; Tania Kümpfel, MD, PhD; Andreas Straube, MD, PhD

Objective.—We tested the hypotheses (i) that autoimmune encephalitis is associated with new-onset headache, and (ii) that the occurrence of headache is associated with the presence of anti-N-methyl-D-aspartate (NMDA)-receptor antibodies.

Background.—Autoimmune encephalitis presents with cognitive dysfunction as well as neuro-psychiatric symptoms. Its pathophysiology might involve antibody-mediated dysfunction of the glutamatergic system as indicated by the presence of anti-NMDA-receptor antibodies in some patients.

From the Department of Neurology, University of Munich Hospital, Großhadern, Munich, Germany (C.J. Schankin, F. Kästele, L. Ann Gerdes, T. Winkler, E. Csanadi, T. Högen, T. Kümpfel, and A. Straube); Institute of Clinical Neuroimmunology, University of Munich Hospital, Großhadern, Munich, Germany (L.A. Gerdes and T. Kümpfel); Department of Neurology, University Medical Center, University of Göttingen, Göttingen, Germany (H. Pellkofer); Department of Clinical Neurophysiology, University Medical Center, University of Göttingen, Göttingen, Germany (W. Paulus); Department of Neurology, University Hospital Bern - Inselspital, University of Bern, Bern, Switzerland (C.J. Schankin).

Address all correspondence to C.J. Schankin, MD, Department of Neurology, University Hospital Bern - Inselspital, University of Bern, Freiburgstrasse 8, CH-3010 Bern, Switzerland, email: christoph.schankin@insel.ch

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Methods.—In this cross-sectional study, patients with autoimmune encephalitis were assessed with a standardized interview for previous headache and headache associated with autoimmune encephalitis. Headache was classified according to the International Classification of Headache Disorders, second edition. Clinical and paraclinical findings were correlated with the occurrence of headache.

Results.—Of 40 patients with autoimmune encephalitis, 19 did not have a history of headache. Of those, nine suffered from encephalitis-associated headache. Seven of these nine had anti-NMDA-receptor antibodies in contrast to only two among the remaining 10 patients without new-onset headache ($P = .023$, odds ratio: 14, 95% confidence interval: 1.5; 127). In most patients headache occurred in attacks on more than 15 days/month, was severe, and of short duration (less than 4 hours). International Headache Society criteria for migraine were met in three patients.

Conclusions.—New-onset headache is a relevant symptom in patients with autoimmune encephalitis who have no history of previous headache, especially in the subgroup with anti-NMDA-receptor antibodies. This indicates a thorough investigation for secondary headaches including anti-NMDA-R antibodies for patients with new-onset headache and neuropsychiatric findings. Glutamatergic dysfunction might be important for the generation of head pain but may only occasionally be sufficient to trigger migraine-like attacks in nonmigraineurs.

Key words: limbic encephalitis, autoimmune encephalitis, anti-NMDA-receptor antibodies, headache, migraine, secondary headache

Abbreviations: NMDA N-methyl-D-aspartate, NMDA-R N-methyl-D-aspartate receptor

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INTRODUCTION

Migraine presents with recurrent attacks of headache,[1] has significant impact on quality of life, and was recently rated number seven of the worldwide causes of disability.[2] Its pathophysiology is complex and might involve a dysfunction of diencephalon or brainstem.[3] It has been hypothesized that the primary events leading to this dysfunction involve cortical spreading depression,[4] a phenomenon shown in animals,[5] which might also exist in humans forming the correlate of typical migraine aura.[6] In animals, inhibition of the glutamatergic N-methyl-D-aspartate (NMDA)-receptor has reduced several parameters of cortical spreading depression, suggesting a major contribution for the generation of migraine aura and/or migraine.[7]

During the past decade a variety of distinct pathogenic autoantibodies against neuronal surface proteins has been identified and broadened the spectrum of autoimmune encephalitis, which can cause limbic encephalitis but may also involve structures outside the limbic system. They can occur in the context of a tumor as a paraneoplastic disease or in the absence of malignancies as primary autoimmune encephalitis. One of the most frequent examples of autoimmune encephalitis relates to antibodies directed against the NMDA-receptor (NMDA-R). Clinically, patients mainly suffer from progressive memory deficits, epileptic seizures, and/or affective symptoms.[8] So far it is unknown if autoimmune encephalitis can cause new-onset headache and if this headache resembles migraine attacks.

While conducting the present study, we systematically studied patients with autoimmune encephalitis. We specifically aimed at describing the frequency and clinical phenotype of new-onset headache. Due to the putative involvement of NMDA-R in the generation of typical migraine aura, we further tested the hypothesis that patients with new-onset headache differ from patients without such headache in the distribution of anti-NMDA-R antibodies. In an exploratory manner, we further assessed whether other clinical or paraclinical parameters are associated with new-onset headache.

MATERIAL AND METHODS

Study Design.—For this cross-sectional explorative study we identified patients between March 2011 and January 2014 at two tertiary hospitals in Germany (Ludwig-Maximilians-University Munich and Georg-August-University Göttingen). Patients were identified either immediately during in-patient treatment of autoimmune encephalitis or by searching electronic records.

Inclusion criterion for the study involved the diagnosis of an autoimmune encephalitis[9] in association with the detection with one of the following antibodies: Hu, Ma1/2, CV2/CRMP-5, Amphiphysin,

LGI1, CASPR2, Contactin-2, GAD, NMDA-R, $GABA_B$-receptor, AMPA-receptor. In accordance with the proposed criteria by Bien et al, patients were also included if no antibodies were detected, but if there was a histopathological diagnosis of autoimmune encephalitis following stereotactic biopsy, demonstration of a tumor within 5 years of symptoms' onset, or an otherwise unexplained temporo-mesial signal increase in T2/FLAIR of typical time course together with the classical clinical presentation (new-onset progressive mnestic syndrome, epileptic seizures, neuropsychiatric abnormalities).[9] Patients were excluded if the clinical routine was indicative for alternative conditions, such as infectious encephalitis, epilepsy, or primary psychiatric disorders.

The study was approved by the ethics committee of the University of Munich (145-10). All subjects gave written informed consent.

Data Collection.—The following data were collected from all patients: clinical characteristics including demographic, modified Rankin-scale score, and diagnostic data, parameters from cerebrospinal fluid investigations, type and titer of antibodies, magnetic resonance imaging (MRI) features, electroencephalography, and response to treatment in respect of headache and neurological outcome. An inflammation in the cerebrospinal fluid was assumed when cell count was >5 cells/μL or protein concentration was >45 mg/dL.

Evaluation of Headache.—Headache was assessed in a personal interview based on the criteria of the International Classification of Headache Disorders, 2nd edition (ICHD-II[1]). We were interested in headache at two different time points: *previous headache* history (beginning more than 5 years prior to symptoms' onset of autoimmune encephalitis) and *recent headache* history (within 1 year of onset, ie, an early symptom of the acute disease). The diagnosis of *headache associated with autoimmune encephalitis* was given according to the definition of secondary headaches in the ICHD-II, when recent headache occurred in a patient without previous headache.[1] In addition, the phenotype of headache was described using the following categories: severity on the verbal rating scale (0-10, with 0 being no pain and 10 being maximum imaginable pain), interference with daily routine or worsening by movement, dynamic (continuous, attacks), frequency (more than daily, daily, more than 15 days/month, 8-14 days/month, 4-7 days/month, 1-3 days/month, less than once/month), duration (seconds to minutes, less than 1 hour, 1-4 hours, 4 hours to 1 day, 1-3 days, 3-7 days, longer than 7 days), character (pulsating, pressing, stabbing), additional symptoms (nausea, vomiting, photophobia, phonophobia), aggravating factors (movement sensitivity, standing, Valsalva maneuver, worse in the morning or at night), location (frontal, temporal, parietal, occipital, laterality), and treatment response.

Statistical Analysis.—Descriptive analysis of clinical data was performed using Microsoft Excel for Macintosh 2011 and IBM SPSS Statistics, version 23. Patients *without previous headache* were stratified according to the presence of new-onset headache in: new-onset headache vs no headache. Both groups were compared using chi-square or Fisher's exact test (in case of expected values <5) for categorical variables, Mann-Whitney *U*-test for ordinal and two-sample *t*-test for interval variables when appropriate. Correlations were assessed using Spearman's rank correlation coefficient. The level of statistical significance was set at $P < .05$. The effect is presented as odds ratio (median and 95% confidence interval).

RESULTS

Clinical Characteristics of Patients.—By searching electronic records, 18 patients with autoimmune encephalitis were identified (median duration between date of diagnosis and interview: 22 months). Twenty-two patients were identified during in-patient treatment, resulting in 40 patients in total (17 female, mean age ± standard deviation: 50 ± 18 years). Clinical characteristics are summarized in Table 1 and can be found in detail in Supporting Information Tables S1 and S2. In 10 patients, medical history by proxy was necessary to obtain a complete clinical picture. Thirty-five had positive antibodies: anti-NMDA-R (n = 15), anti-Hu (n = 3), anti-LGI1 (n = 6), anti-Ma1 (n = 2), anti-Ma2 (n = 2), anti-CASPR2 (n = 3), and anti-GAD (n = 2); one patient had both anti-NMDA and anti-LGI1; and one had both anti-CV2 and anti-CASPR2. Of the remaining five, one patient had biopsy-proven autoimmune encephalitis, another one was diagnosed with Hodgkin lymphoma and malignant melanoma after

Table 1.—Summary of Clinical Characteristics of Patients With Autoimmune Encephalitis Stratified in Three Subgroups According to the Previous History of Headache and New Onset of Headache (Data Derived from Supporting Information Tables S1 and S2)

	Patients With Autoimmune Encephalitis n = 40				
		No Previous Headache n = 19			
	Previous Headache n = 21	No Current Headache n = 10	New-Onset Headache n = 9	No Current Headache vs New-Onset Headache *P* value	Previous Headache vs No Previous Headache *P* value
Mean age at onset ± SD	49 ± 15	55 ± 19	49 ± 23	.52	.59
Gender female	9	5	3	.65	.96
Family history of headache	10	1 (of 8)	2 (of 8)	1.00	.09
Median mRS at onset	3	3	3	.19	.87
Median mRS outcome	2	2	3	.20	.98
Response of encephalitis to treatment	14 (of 16)	7 (of 9)	5	.62	.23
Anti-NMDA receptor antibodies	7	2	7	**.023**	.37
Other than anti-NMDA receptor antibodies	12	6	1	.06	.20
Anti-Hu antibodies	1	1	1	1.00	.60
Anti-LGI1 antibodies	5	2	0	.47	.41
Anti-CASPR2 antibody	2	2	0	.47	1.00
Anti-Ma1 antibody	2	0	0	1.00	.49
Anti-Ma2 antibody	0	2	0	.47	.22
Anti-CV2 antibody	0	1	0	1.00	.48
Anti-GAD antibody	2	0	0	1.00	.49
No antibody	2	2	1	1.00	.65
Epileptic seizures	12	8	5	.35	.46
MRI lesion in temporal lobe	14	7	3	.18	.37
CSF inflammation (>5 cells/μL or protein > 45 mg/dL)	14 (of 20)	5	6	.65	.62

The assessment of a correlation between presence of anti-NMDA-R antibodies and the occurrence of new-onset headache was predefined ($P = .023$, odds ratio 14, 95% confidence interval: 1.5; 127, two-tailed Fisher's exact test). mRS Modified Rankin-scale score.

onset of neurological symptoms, and three had typical history and typical magnetic resonance imaging-findings (patients 8, 10, and 22).

Twenty-one patients had a previous history of either migraine, tension-type headache, or a mixture of both. Of the remaining 19 patients, nine reported new-onset headache, ie, *headache associated with autoimmune encephalitis*. Phenotypically, four of these met criteria for tension-type headache (patients 3, 22, 25, 28), three for migraine (patients 1, 13, 34, all had anti-NMDA-R antibodies; Supporting Information Table S2), and two could not be classified according to the ICHD-II[1]: patient 15 did not meet criteria for tension-type headache due to a severity of more than 6 out of 10 on the verbal rating scale, interference with daily routine and unilateral location, and patient 39 did not meet criteria for migraine due to a short duration of less than 4 hours, and the lack of photophobia, phonophobia, nausea, and/or vomiting. The phenotype of all patients with *headache associated with autoimmune encephalitis* is shown in Table 2. When looking at all patients together, headache was either continuous (n = 3) or, if episodic, manifested with frequent attacks (daily or more frequent in 5 of 6) of short duration (less than 4 hours in 4 of 6). Intensity was

Table 2.—— Headache Characteristics of Patients With *Headache Associated With Autoimmune Encephalitis*

Patient	Severity	Interference with Daily Routine or Worsening by Movement	Dynamic	Frequency of Attacks	Duration of Attacks	Pain Character			Addi-tional Symptoms		Aggravating Factors					Location		Treatment Response H/E
	VRS (1-10)					Pulsating	Pressing	Stabbing	N/V	P/P	Movement sensitivity	Standing	Valsalva manoeuvre	Worse in the morning	Worse at night			
1	8	+	Attacks	>1/day	*A	−	+	−	+	−	−	+	−	+	−	bilat.	parietal	−/−
3	6	−	Attacks	>15 days/ month	<1 day	−	+	−	−	−	−	+	−	*B	*B	unilat. right	fronto-temporal	+/+
13	10	+	Continuous			−	+	+	+	+	+	+	+	−	+	bilat.	fronto-temporal	+/+
15	10	+	Continuous			*C	*C	*C	−	−	−	−	−	*C	*C	unilat. right	hemi-cranial	*D
22	10	+	Attacks	>1/day	<1 hour	−	+	−	−	−	+	+	−	+	−	bilat.	temporal	+/+
25	5	−	Attacks	daily	<4 hours	−	+	−	−	−	−	+	−	+	−	bilat.	holo-cephal	+/+
28	*C	−	Attacks	>15 days/ month	<4 hours	*C	*C	−	−	−	−	−	−	−	*C	bilat.	parietal	*D
34	7	+	Continuous			−	−	+	+	−	+	−	−	−	−	unilat.	occipito-nuchal	+/+
39	9	+	Attacks	>1/day	<4 hours	+	−	−	−	−	−	−	−	−	−	unilat. left	fronto-temporal	−/−

Treatment response H/E-Headache/Encephalitis improved after treatment of limbic encephalitis.
P/P-Photophobia and/or phonophobia.
*A-Not known because patient always took pain medication.
*B-Worse at noon.
*C-Not recalled by patient.
*D-Lost to follow-up.

severe (more than 6 of 10 on the verbal rating scale in 6 of 9), of pressing quality (5 of 9), interfering with daily routine (5 of 9), and without migraine-typical features (in 6 of 9). It has to be noted that one third met criteria for migraine with only one of those having a positive family history of migraine. Headache responded well to pain medication (in 6 of 9) as well as to standard treatment of autoimmune encephalitis (steroids, immunoadsorption, plasmapheresis, rituximab) in five patients (56%). All of the latter five also improved with other symptoms of their autoimmune encephalitis. In contrast, two of the remaining four neither responded in respect to encephalitis or headache. Of the 21 patients with previous headache history, only patients 3, 4, and 20 reported amelioration of headache whereas 15 patients did not report a change in headache (three lost to follow-up), although 19 improved in respect of autoimmune encephalitis (one did not improve, one lost to follow-up; Supporting Information Table S1).

In the group of patients without previous headache history, patients with *headache associated with autoimmune encephalitis* differed from those without in respect of the presence of anti-NMDA-R antibodies (Table 1). There was no association between the presence of anti-NMDA-R antibodies and signs of inflammation in the cerebrospinal fluid (ie, cell count >5/μL or protein >45 mg/dL; Supporting Information Table S2) for the group without previous headache history (n = 19, $P = .170$, Fisher's exact test) and all patients (n = 39, one missing CSF, $P = .171$, Fisher's exact test). Further, the cerebrospinal fluid count in the group with new-onset headache did not differ from the group without ($P = .09$, Mann-Whitney *U*-test; Supporting Information Tables S1 and S2). There was no correlation between disease severity (assessed with modified Rankin-scale score) and headache prevalence (Table 1) or headache severity (assessed within the subgroup of patients with new-onset headache (Spearman's rank correlation coefficient $R = -0.12$, $P = .76$; Table 2 and Supporting Information Table S1).

Autoimmune encephalitis does not represent a single entity. One major stratifying parameter is whether antibodies are directed against cell surface or intracellular antigens.[10] Taking this into account, new-onset headache remained associated with anti-NMDA-R antibodies even when assessing only the subgroup of patients with antibodies directed against cell surface antigens alone (Table 2 and Supporting Information Tables S1 and S2): of all patients without previous headache history, nine had anti-NMDA-R antibodies (seven had new-onset headache), two had anti-LGI1 antibodies (no headache), and one had anti-CASPR2 antibodies (no headache). The subgroup with new-onset headache still differed from the subgroup without in respect of presence of anti-NMDA-R antibodies ($P = .045$, Fisher's exact test).

DISCUSSION

To the best of our knowledge, this study represents one of the largest groups of patients with autoimmune encephalitis investigated for secondary headache. A limitation, however, is the still small number of just 19 subjects in the group of patients without previous headache history, which might narrow the generalizability of our findings. However, the correlation between new-onset headache and presence of anti-NMDA-R antibodies was assessed in a predefined manner reducing the risk of type 1 error.

In the group of patients without previous history of headache (n = 19), we found nine patients who developed a new-onset headache. Terming this *headache associated with autoimmune encephalitis* is strongly supported by the finding that headache improved only when treatment of other symptoms associated with the encephalitis was also successful as in general required for secondary headaches by the ICHD-II.[1] Importantly, in the group of patients with previous headache history, there was no such response of headache to treatment, suggesting a different mechanism. Headache thus seems to be an important symptom of autoimmune/limbic encephalitis as already mentioned previously.[8,11,12]

Among our subjects with such new-onset headache, almost all patients had anti-NMDA-R antibodies. In contrast, most patients without history of headache and non-anti-NMDA-R encephalitis did not develop headache. This association remained

significant when looking solely at patients with antibodies directed against cell surface antigens speaking against a bias introduced by intermingling different subgroups of autoimmune disorders in our study.

In the disease-defining studies of anti-NMDA-R-associated encephalitis, headache was mentioned in the unspecific prodromal phase.[8] Except for some case reports[13] headache has not been in the focus of previous publications, probably due to the dominating severity of other neurological and psychiatric symptoms, and hypotheses of the underlying mechanism are scarce. Typical other causes for unspecific secondary headache, such as cerebrospinal fluid inflammation (pleocytosis, elevated protein)[1] or epileptic seizures,[14] were equally distributed when comparing the subgroup with new-onset headache with the group without. Similarly, a mechanism of unspecific meningeal irritation in patients with headache and anti-NMDA-R antibodies seems unlikely since there was no correlation between presence of anti-NMDA-R antibodies and signs of cerebrospinal fluid inflammation. In contrast, the mechanism of such new-onset headache might involve hyperexcitability of the brain. A variety of NMDA-R antagonists, such as ketamine, are used for the treatment of pain,[15] and animal research with NMDA-R inhibition has *reduced* cortical spreading depression,[7] which is thought to be a fundamental mechanism of migraine aura.[4] Furthermore, migraine patients with prolonged aura showed improvement of aura severity by intranasal application of ketamine.[16] In contrast to such brief pharmacological inhibition of NMDA-R function, anti-NMDA-R antibodies in limbic encephalitis were shown to internalize the receptor,[17] resulting in inactivation of inhibitory GABAergic neurons (ie, disinhibition or glutamatergic hyperactivity),[18,19] possibly *facilitating* cortical spreading depression.[20] A report on a patient with previous history of migraine with visual aura who had prolonged episodes of a left hemispheric syndrome and headache in association with anti-NMDA-R encephalitis[13] is consistent with such aggravation of cortical spreading depression. Spreading depression in the hippocampus has also been reported,[21] resulting in activation of the caudal trigeminal nucleus.[22] This, the main presence of NMDA-R in the hippocampus,[23] and its structural and functional alteration in patients with NMDA-R autoimmune encephalitis,[24,25] might indicate a major role for the generation of head pain in our patients. Due to the non-migrainous phenotype of headache in our study, such events of spreading depression, however, might not be sufficient to cause migraine attacks suggesting that headache in anti-NMDA-R antibody-associated encephalitis is a unique headache syndrome.[3]

Whether headache is an early symptom of anti-NMDA-R encephalitis could not be assessed in this study due to its cross-sectional design. Further, the retrospective design might bear the risk of recall bias due to the neuropsychological deficit of some patients.[8] Therefore, prospective studies would be necessary to confirm our findings. Long-term data would be interesting to see whether patients develop a headache disorder, ie, a continuing headache problem despite successful treatment of the encephalitis. Our data do not indicate a correlation between severity of the encephalitis (based on the modified Rankin-scale score) and the occurrence of headache. It is, therefore, possible that patients might have mild forms of anti-NMDA-R encephalitis who are predominantly affected by headache with only minor symptoms of cognitive dysfunction as reported for patients with psychiatric symptoms.[26] Concentration problems, tiredness, and mood changes are premonitory-like symptoms of migraine[27] and chronic migraine. However, headache patients without a history of migraine or with new-onset headache without typical migraine features should not have such cognitive symptoms. In particular, this might be important for the diagnostic work-up of patients with 'new daily persistent headache,' ie, ICHD-II code 4.8.[1] We would therefore hypothesize that investigating for secondary headaches might be important in patients with significant *new-onset* headache, especially when frequent, of severe intensity and associated with – even mild – signs of encephalopathy, such as concentration problems, psychomotor slowing or memory deficits. According to this study, careful clinical examination, brain imaging, and liberal laboratory testing including anti-NMDA-R determination in the cerebrospinal fluid might be considered in such

patients with (chronic) headache of unknown origin. The therapeutic strategy in patients with a positive anti-NMDA-R antibody titer remains to be determined. Two thirds of our patients also responded to pain medication, but immunosuppressive therapy might be of particular importance against the background of the potentially nonreversible cognitive deficits of patients with autoimmune encephalitis in case of delayed treatment.[28]

CONCLUSION

New-onset headache can be an important symptom in patients with autoimmune encephalitis, especially when anti-NMDA-receptors are involved. In our patients, such headache was either continuous or manifested with frequent attacks (daily or more frequent) of short duration, severe intensity, pressing quality, and interference with daily routine. Typical migraine features can be missing. If our data can be confirmed in future studies, patients with new-onset headache and signs of even mild cognitive dysfunction might have to undergo careful evaluation for secondary headaches including lumbar puncture and determination of anti-NMDA-receptor antibodies. The consequence of a positive anti-NMDA-receptor antibody in respect of treatment has not been studied here, and the role of immunomodulatory therapy remains unsettled.

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STATEMENT OF AUTHORSHIP

Category 1

(a) Conception and Design

Christoph J. Schankin, Andreas Straube

(b) Acquisition of Data

Christoph J. Schankin, Fabian Kästele, Lisa Ann Gerdes, Tobias Winkler, Endy Csanadi, Tobias Högen, Hannah Pellkofer, Walter Paulus, Tania Kümpfel, Andreas Straube

(c) Analysis and Interpretation of Data

Christoph J. Schankin, Fabian Kästele, Walter Paulus, Tania Kümpfel, Andreas Straube

Category 2

(a) Drafting the Manuscript

Christoph J. Schankin

(b) Revising It for Intellectual Content

Fabian Kästele, Lisa Ann Gerdes, Tobias Winkler, Endy Csanadi, Tobias Högen, Hannah Pellkofer, Walter Paulus, Tania Kümpfel, Andreas Straube

Category 3

(a) Final Approval of the Completed Manuscript

Christoph J. Schankin, Fabian Kästele, Lisa Ann Gerdes, Tobias Winkler, Endy Csanadi, Tobias Högen, Hannah Pellkofer, Walter Paulus, Tania Kümpfel, Andreas Straube

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SUPPORTING INFORMATION

Additional Supporting Information may be found in the online version of this article.

Table S1.—Clinical characteristics of all patients (including subjective improvement that does not necessarily reflect in a reduction of modified Rankin-scale score).

Table S2.—Autoimmune encephalitis was diagnosed based on the presence of antibodies, typical MRI-findings, tumour occurrence, and evidence of autoimmune encephalitis in brain biopsy. The table further shows the earliest cerebrospinal fluid findings of the study population.