Treatment of immune-mediated temporal lobe epilepsy with GAD antibodies[☆]

M.P. Malter [a,e,1,*], C. Frisch [a,1], H. Zeitler [b,1], R. Surges [a,1], H. Urbach [c,1], C. Helmstaedter [a,1], C.E. Elger [a,1], C.G. Bien [a,d,1]

[a] University of Bonn Medical Centre, Department of Epileptology, Germany
[b] University of Bonn Medical Centre, Department of Internal Medicine, Germany
[c] University Medical Centre Freiburg, Department of Neuroradiology, Germany
[d] Epilepsy Centre Bethel, Krankenhaus Mara, Bielefeld, Germany
[e] University Hospital Cologne, Department of Neurology, Germany

A R T I C L E   I N F O

A B S T R A C T

Purpose: Temporal lobe epilepsy with antibodies (abs) against the glutamic acid decarboxylase 65 isoform (GAD-TLE) is known as an immune-mediated neurological syndrome. Here we evaluate the therapy response to various immunotherapies and epilepsy surgery in this syndrome.
Method: All patients with GAD-TLE and follow-up data and stored serum and CSF samples, identified and treated at the Bonn centre from 2002 to 2010, were studied retrospectively. Seizure freedom for ≥ 1 year and reduction of $\geq 50\%$, i.e. therapy response, were assessed. GAD-ab titres and neuropsychological performances were documented prior and after individual interventions.
Results: Thirteen patients with GAD-TLE were identified with the following seizure responses: corticosteroids (5 responders out of 11 treated patients); i.v. immunoglobulins (1/5), apheresis therapy (1/8); and natalizumab (1/1), selective amygdala-hippocampectomy (2/3). None of the patients achieved sustained seizure freedom apart from one patient. This patient was on antiepileptic drug treatment after discontinuation of immunotherapy.
Conclusion: The seizure response to immunotherapies in patients with GAD-TLE was poor. Corticosteroids were the most effective regarding seizure response. Especially the poor effects of apheresis therapies support the idea that GAD-abs are not directly pathogenic. None of three patients was seizure-free after temporal lobe surgery suggesting that GAD-TLE patients respond worse than others to this type of intervention. Our results reflect the chronic course of the disease with low likelihood for patients with GAD-TLE to attain long-term seizure freedom.

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1. Introduction

Glutamic acid decarboxylase (GAD) catalyzes the synthesis of gamma aminobutyric acid (GABA), the major inhibitory neuro-transmitter in the central nervous system. Antibodies (abs) against the GAD65 isoform are markers for insulin dependent diabetes mellitus and – if present at high titres – immune-mediated neurological syndromes such as stiff-person-syndrome [1], cerebellar ataxia [2], as well as limbic encephalitis (LE) and temporal lobe epilepsy (TLE) in adults [3–5] and children [6,7]. "Subacute" LE with GAD-abs and "chronic" TLE with GAD-abs have been suggested to be two ends of one spectrum of an immune-mediated mediotemporal lobe disorder. A plausible explanation for these two "poles" is that in early stages the condition appears as "LE" and later on as chronic epilepsy [8]. To overcome terminological inconsistencies, here we use the term "immune-mediated temporal lobe epilepsy with GAD-abs" (GAD-TLE) irrespective of disease duration and "acuity". Symptoms consist of temporal lobe seizures, memory and mood disturbances.

In our former publications [5,9], patients with GAD-TLE had a worse outcome than patients with abs against the voltage gated potassium channel (VGKC) complex despite similar immunother-apeutic interventions (usually monthly i.v.-methylprednisolone

pulses in dosages of 500–1000 mg/day on 3–5 consecutive days). Because none of the patients with GAD-TLE became seizure-free, a more chronic course of the disease has been suggested. Furthermore, direct pathogenicity of GAD-abs is still discussed controversially [10–12]. One would expect that in case of direct involvement of GAD-abs in pathogenic processes, their reduction should prompt clinical improvement.

Here, we report retrospectively our single centre experience in treatment of GAD-TLE. The patients reported here have been treated a few years after the first publications of the good treatability of encephalitides with abs against the VGKC-complex [13] or the N-methyl-D-aspartate receptor (NMDAR) [14]. There was a great optimism that any ab associated autoimmune encephalitis – including those with GAD-abs – would respond to adequate and consequent immunological therapy. Here we evaluate the therapy response to various immunotherapies and epilepsy surgery in patients with GAD-TLE regarding seizure frequency reduction and, if available, memory outcome.

2. Methods

2.1. Study cohort

All patients with GAD-TLE with available follow-up data and with stored serum and CSF samples for ab re-testing, studied from 2002 to 2010 at the University of Bonn, Department of Epileptology, were included in this retrospective report. The diagnosis was based on clinical features of seizures of temporal semiology and evidence of high titre serum GAD-abs (>1:2000 in accordance with a previous suggestion [15]).

The ab diagnosis was made by use of indirect immunohistochemistry with confirmation through radioimmunoprecipitation (done by Angela Vincent, Oxford/UK). Abs against the other antigens available for routine testing at that time, i.e. against the VGKC complex, against the NMDAR and against onconeural antigens Hu, Ma, amphiphysin, CV2/CRMP5 were excluded. All available serum and CSF samples were re-tested for this study by cell-based assays with acetone fixed HEK cells transfected with GAD65 (Euroimmun, Luebeck/Germany, performed by CGB). The protocol for indirect immunofluorescence follows the recommendations given by Euroimmun (FA 112d-1005-1, IgG) with few modifications: the buffer was PBS (Euroimmun: PBS-Tween); the secondary system consisted of a goat-anti-human IgG (heavy and light chain) ab conjugated with DyLight 594 produced by Jackson ImmunoResearch, West Grove, PA, USA, Code No. 109-515-088 at a dilution of 1:100 (Euroimmun: goat-anti-human IgG, conjugated with fluorescein, no further information given); nuclear counterstaining with Hoechst 33342 at 1:10,000 (Euroimmun: no nuclear staining); embedding with 1,4-diazabicyclo[2.2.2]octan (Euroimmun: glycerol). The stained cells are examined using a fluorescence microscope (Leica DM 2000; Wetzlar, Germany) with excitation at 592 nm and emission filter at 616 nm for bound ab and 350/462 nm for the nuclear counterstain. An endpoint titration was done by serial dilutions in a multiple of 1:2. The titre is the concentration at which a signal is just still detectable in comparison with adjacently stained non-transfected cells. Each titration is rated by two independent investigators. If the ratings are divergent, the mean of the two ratings is recorded. The antibody index (AI, i.e., the ratio between the CSF/serum quotients of GAD-ab titres and total IgG concentrations) indicates whether antibodies are produced intrathecally. We took an AI > 4 as an indication of intrathecal production of the specific antibody [16].

Clinical and paraclinical data were obtained from the patient records. Comorbidities were evaluated both at visit 1 and last follow-up. Tumour searches were performed in all patients according to a dedicated protocol at visit 1 [17]. For brain MRIs,

a dedicated epilepsy protocol [18] was used on a 3 Tesla scanner, Philips, The Netherlands (Dept. of Neuroradiology) or a 3 Tesla "Trio" scanner from Siemens, Erlangen, Germany (Life&Brain Institute). If available previous brain MRIs from other institutions were re-assessed. MRI courses were observed at visit 1 and at last available follow up to reveal changes on long-term follow up, especially newly developed hippocampal atrophies. All images were re-evaluated for this study.

Eight patients were part of our previous study [5], except from one all with extended follow-up data in the present study. Some patients were included in the study by Wagner, dealing with morphological changes on MRI without clinical data reported [19].

2.2. Therapeutic interventions

Most patients received multiple therapeutic interventions in different chronological sequences. All patients were on antiepileptic drugs, immunotherapeutic interventions and epilepsy surgery were added on this. Only one intervention was delivered in an individual patient at the same time. We analyzed the outcome of each single therapeutic intervention (regardless of the chronological order of administration in the individual patient) and grouped them as follows: corticosteroids, intravenous immunoglobulins (IVIG), apheresis techniques (plasma exchange or immunoadsorption), natalizumab, epilepsy surgery. Some patients received temporarily only antiepileptic drugs (AED) without any other intervention, therapy response in these periods were observed as well. Azathioprine (Aza) and mycophenolat-mofetil (MMF) were given as oral long-term immunosuppressants in some patients subsequent to immunotherapies or epilepsy surgery. Their use was considered as supportive treatment and not included in further analysis.

2.3. Immunotherapy regimens

Immunotherapies were delivered as off-label individual treatment attempts after obtaining informed patient consent (compassionate use).

2.3.1. Corticosteroids
They were given as monthly i.v.-methylprednisolone (MP) pulses (500–1000 mg/day on 3–5 consecutive days) or continuously per os with initial standard doses of 100 mg/day. The decision on therapy duration and long-term dosage was made individually. To characterize the "intensity" of each intervention, corticosteroid doses were expressed as MP-equivalent doses (prednisone or prednisolone doses were multiplied by 0.8 [20]).

2.3.2. IVIG
IVIG were given at doses of 0.4/kg body-weight/day. They were delivered in monthly pulses, initially starting with sequences of three to five doses on consecutive days and thereafter monthly single day pulses in the following. Total doses were calculated to characterize the "intensity" of each intervention.

2.3.3. Apheresis therapy
This was performed as plasmapheresis or immunoadsorption according to commonly accepted principles. In four patients immunoadsorption was combined with continuous lumbar CSF drainage over 4 days with maximal drain of 150 ml/day (a simplified version of Wollinsky's liquorpheresis or CSF-filtration [21,22]) based on the assumption that a removal of the ab-containing CSF could reduce ab load in the CNS.

2.3.4. Natalizumab
It was used similar to the therapy regimen in multiple sclerosis with monthly single day infusions of 300 mg i.v. Before initiation of

this therapy the previous immunotherapy was terminated 3 months before and infectious causes were re-evaluated extensively in serum and CSF. Infusions were given on an in-patient basis.

2.4. AED

AED treatment was administered in all patients according to generally clinically accepted principles at the discretion of the treating physician to achieve maximum seizure control and tolerability. Changes were made in cases of intolerabilities or lack of effectiveness. Some patients received only AEDs for a period because efficacy of immunotherapy was assumed low and was discontinued therefore.

2.5. Epilepsy surgery

Selective amygdalo-hippocampectomy was offered to selected drug-resistant patients after comprehensive presurgical diagnostics according to generally accepted standards [23].

2.6. Outcome parameter

In each patient, periods with the above tabulated therapeutic interventions were retrospectively defined from the patient records. Outcome variables were seizure frequency and, where available, memory outcome and ab titre changes.

2.6.1. Seizure frequency

The number of all documented seizures in the month prior and after a therapeutic intervention was taken from patient diaries or – if unavailable – from frequency estimates of the patients and their relatives. Seizure frequency reduction of $\geq 50\%$ was considered as treatment response. Seizure freedom was rated as completely seizure-free including auras (Engel class IA [24]) for at least 12 months [25].

2.6.2. Memory performance

Neuropsychological testing was performed at timepoints prior to and after immunological interventions. Tests regularly comprised memory capacities indicative of temporal lobe functions. For verbal memory (VM) capacities the Verbal Learning and Memory Test (a German adaptation of the Rey Auditory Verbal Learning Test [26]) and for figural memory (FM) assessment the *Diagnostikum für Cerebralschädigung*, revised version [27], were used. To condense the information from these tests, data were transformed into a single summary score representative for the respective memory domain as described in detail before [5]. A performance below one standard deviation (SD) of normal controls was classified as abnormal. For follow-up ratings, individual changes in performance were categorized using reliable change indices according to previous proposals. Relevant improvement was classified as change from abnormal to normal values. Deterioration was defined as change from normal to abnormal capacities.

2.7. Statistics

For numerical data in memory tests before and after an intervention, a paired-*t*-test was used. *P*-values < 0.05 (two-tailed) were considered as significant.

3. Results

3.1. Visit 1

Thirteen patients were identified. For individual patient characteristics see Table 1. Most of the patients (85%) were females with a median age at disease onset of 24 years (range: 8–47) and median disease duration of 18 months (range 1–252). All patients had clinical seizures (median: 10/month, range 1–150). Memory functions were impaired in the majority of patients (77%), often in both domains (46%). Only three patients, however, were in the range less than −1 standard deviation of normal controls, i.e., most were impaired, but not severely. MRI features revealing mediotemporal T2/FLAIR signal increase and swelling compatible with limbic encephalitis were observed in all patients with GAD-TLE at visit 1 or in previous MRIs. MRI abnormalities were unilateral (85%) or bilateral (15%). In two patients selective amygdalo-hippocampectomy was performed prior to the diagnosis of GAD-abs and prior to visit 1 (details are given below, Section 3.3). One patient had right sided swelling and left-sided hippocampal atrophy at visit 1. In this patient, previous MRIs were congruent with a left-sided encephalitic mediotemporal onset before atrophy. Additional bilateral hyperintense lesions outside the mediotemporal structures were seen in three patients: in thalamus and insula, in the depth of cortical sulci and around the fourth ventricle. Serum titres ranged from 1:2000 to 1:64,000, CSF titres from 1:16 to 1:1000. Abs were synthesized intrathecally in 77% of the patients.

3.2. Response to individual therapeutic interventions

3.2.1. Immunotherapies (N = 13)

An overview of the performed therapy regimens and their chronological sequences in individual patients is given in Fig. 1. Concomitant AED treatment was conducted in all patients. MP pulses were the most frequent applied immunotherapy (77%), in 62% as first immunotherapy.

3.2.1.1. Corticosteroids (N = 11). The corticosteroid interventions lasted for a median of 4 months (1–7 months). The median total dose was 19 g methylprednisolone equivalent (3–30 g). Five patients (45%) responded to corticosteroid therapy. One patient gained short-time seizure-freedom for one month, but treatment had to be changed due to relevant hyperglycaemia. Subsequently, this patient developed insulin dependent diabetes mellitus. Neuropsychologically, there was no group effect for memory changes under therapy (*t*-test pre vs. post, N = 7). On an individual level improvement was only seen for FM in one patient, whereas deterioration in FM was seen in another patient as well. Serum titres changed by a median of −50% (−88% to −0%; N = 5), CSF titres remained stable in two patients and went down by 88% in one patient. Notably, adverse events were observed in six patients (55%): Cushing syndrome in three patients (50%), hyperglycaemia (evolving into diabetes mellitus, probably GAD ab related), sleep disorders, nervousness and psychosis in one patient each.

3.2.1.2. IVIG (N = 5). This intervention was performed for a median of 3 months (2–5 months). The patients received a median total dose of 3 g/kg body weight (range 3–4 g). A seizure response was only observed in one patient (20%). Again, memory changes (N = 3) were without group effect (*t*-test: n.s.) and one patient deteriorated in FM on an individual level. GAD-ab titres changed by −50% and 0% where tested; CSF titres changed in the respective patients by 0% and +300%. Treatment was well tolerated in all cases.

3.2.1.3. Apheresis therapy (N = 8). Eight patients underwent immunoadsorption. Three out of eight patients underwent one or two sequences of 9, 10 and 20 plasmapheresis sessions before (median duration 1 months, range 1–2 months). This had no effect on seizure frequency. Hence, therapy was switched to immunoadsorption in these three cases. Immunoadsorption was performed as sequence of 16 sessions in median (range: 11–26) each (median

Table 1
Individual patient characteristics at visit 1 and follow up in GAD-TLE patients.

Visit 1	Gender/age at onset (years)	Disease duration (mo)	No of sz/mo	Memory deficits	MRI swelling	MRI atrophy	AED	Co-morbid.	FU period (month)	Main IT[a]	Supportive IT	SAH	No. of sz/mo	Memory deficits	Ab titres serum	Ab titres CSF	MRI swelling	MRI atrophy	AED	Co-morbid.
1	F, 23	10	8	VM, FM	L	SAH R	1	–	84	MP, IVIG	Aza	R	2	VM, FM	+	+	L	SAH R	4	IDDM, SLS
2	F, 47	21	12	VM, FM	RL	–	1	–	40	MP, PEX, IA,	Cyc, MMF	–	2	VM	+	+	L	–	2	–
3	F, 24	16	8	VM	L	–	2	–	12	MP	–	–	0.2	VM, FM	+	n.d.	N	–	2	–
4	F, 18	1	1	VM, FM	R	–	1	–	34	MP, IA	Cyc, MMF	–	0	VM, FM	+	n.d.	RL	–	2	–
5	F, 20	40	150	–	RL	–	1	–	55	MP	–	–	30	–	+	n.d.	RL	–	3	–
6	F, 21	54	10	–	R	L	2	SLS	39	IVIG, IA,	Cyc, MMF	–	5	–	+	–	R	L	3	SLS
7	M, 26	4	135	–	L	–	0	IDDM	39	MP	–	–	30	–	+	–	L	–	2	IDDM
8	F, 17	18	30	FM	R	–	2	–	51	MP, IVIG, IA, Nata	MMF	–	5	–	+	–	R	–	2	–
9	F, 43	8	6	FM	L	–	1	–	26	PEX, IA	Cyc	L	8	VM	+	+	RL	–	2	–
10	F, 8	252	3	VM, FM	R	SAH L	3	–	37	MP, IVIG, PEX, IA	Cyc, Aza	L	20	–	+	+	R	SAH L	3	–
11	M, 30	240	8	VM, FM	R	–	2	–	22	MP, IA	MMF	–	1	VM	+	n.d.	R	–	3	–
12	F, 24	100	30	FM	L	–	1	–	22	IVIG, MP	MP	–	20	FM	+	+	RL	–	3	–
13	F, 24	5	150	VM, FM	L	–	0	–	27	MP, IA	Cyc, Aza, MMF	L	2	n.d.	n.d.	+	SAH L	–	2	–
Medians (range)	24 (8–47)	18 (1–252)	10 (1–150)				1 (0–3)		37 (12–84)	2 (1–4)			5 (0–60)						2 (2–4)	

Mo, month; sz, seizure; AED, antiepileptic drugs; VM, verbal memory; FM, figural memory; R, right; L, left; FU, follow-up; IT, immunotreatment; MP, methylprednisolone; IVIG, i.v. immunoglobulines; IA, immunoadsorption; SAH, selective amygdalo-hippocampectomy; Nata, Natalizumab; Cyc, cyclophosphamid; Aza, azathioprin; MMF, mycophenylat-mofetil; IDDM, insulin dependent diabetes mellitus; SLS, stiff limb syndrome.
[a] Listed in chronological sequence.

Fig. 1. Immunotherapies in chronological sequence in individual GAD-TLE patients. SAH, selective amygdalo-hippocampectomy; IVIG, intravenous immunoglobulines; PEX, plasmapheresis; IA, immunoabsorption; Nata, natalizumab; BW, body weight.

number of sequences: 1, range 1–2), always in conjunction with immunosuppression in form of oral prednisolone and/or cyclophosphamide or mycophenolate mofetil. Half of the patients underwent immunoadsorption combined with CSF drainage (N = 4). This was not superior in seizure frequency reduction. Among the eight patients with immunoadsorption, one was a responder (13%). Memory parameters did not reveal group effects (t-test: n.s.). On individual levels, VM and FM deteriorated each in one patient, FM improved in one patient. Median changes of GAD-abs were −75% in serum (−100% to −50%, N = 7) and −25% in CSF (−75% to +56%, N = 8). All patients with CSF drainage refused a second cycle because of dorsal pain or feeling uncomfortable with this therapy. No further relevant adverse events were seen during immunoadsorption.

3.2.1.4. Natalizumab (N = 1). One patient was treated with 1.2 g natalizumab for three months with good seizure response but without memory changes. GAD-ab titres were not available. Despite seizure response without adverse events, treatment was discontinued because of new insights in the meantime regarding elevated risk for progressive multifocal leukencephalopathy (PML) in patients with previously received immunosuppressants [28].

3.3. Epilepsy surgery (N = 3)

Three patients underwent selective amygdalo-hippocampectomy because of medically intractable seizures. In only one of these, diagnosis of GAD-TLE was known at the time of decision for surgery. In the other two patients, surgery was performed prior to visit 1. Routine histopathological evaluation of two surgical specimens revealed lymphocytic T-cell infiltration compatible with chronic encephalitis. These patients had a relevant seizure frequency reduction after surgery, but achieved no seizure freedom (Engel IIA). The third patient with normal histopathology was the one with the maximum disease duration of 10.6 years at time of surgery and was not treated with immunosuppressants after surgery. She had no improvement in seizure control after surgery.

3.4. AEDs only (N = 7)

One of these seven patients (14%) had not just seizure frequency reduction ≥50% but was even seizure free for 17 months at last

follow up with persistently positive GAD-ab titres (Engel IA). On the other hand, two patients deteriorated in seizure frequency after discontinuation of immunotherapy. One of them had been operated before (No. 1) with encephalitic histopathology. Subsequently to termination of oral steroids 20 months after operation (Engel IIA), encephalitis relapsed in contralateral mediotemporal structures. The patient recovered after re-initiation of several immunotherapies but did not regain previous outcome level (Case vignette in Ref. [29]).

3.5. Last follow up

For individual outcomes, see Table 1. At last available follow up (median: 34 months, range 6–84) after a median of two immunological interventions (range 1–4) and three epilepsy surgery procedures, 10 patients (91%) had ≥50% seizure frequency reduction as compared to visit 1, but only one patient (8%) was seizure-free for at least 12 months (patient No. 4). He was on AEDs only after discontinuation of immunotherapy.

Memory outcome data at last follow up were available in 12/13 patients. Individual changes from pathological to normal memory performance were only seen in five patients for FM. No group effects were observed comparing VM and FM at visit 1 and follow up (*t*-test: visit1 vs. follow up).

Among the available materials, only one serum became GAD-ab-negative.

MRI was available in 12 patients at last available follow up: in three patients (25%) mediotemporal encephalitic MRI features had evolved from unilateral to bilateral. In two, MRI abnormalities had regressed from bilateral to unilateral. The remaining seven patients were unchanged. None of the patients developed hippocampal atrophy during the follow up period.

Insulin dependent diabetes mellitus and stiff-person-syndrome newly occurred as GAD ab associated comorbidities in one patient during follow up period. None of the patients had a tumour detected.

4. Discussion

In GAD-TLE we observed a poor responsiveness of seizures to several immunotherapies and epilepsy surgery as add-on interventions to standard AED therapy. Only one out of 13 patients achieved seizure freedom for ≥12 months at last follow-up. Seizure response (≥50% reduction) was most frequently achieved under corticosteroids (45% of patients) with no apparent or beneficial effects on memory function. However, relevant side effects were observed in 50% of the patients. IVIG were less effective in seizure response (20%) but with better tolerability than corticosteroids. Clinical benefit under apheresis therapies was poor. Natalizumab was helpful in the one treated case, but treatment (and response) could not be maintained due to discontinuation of the therapy because of concern about PML. Memory outcome, too, was not significantly affected by any treatment regimen. GAD-ab titres declined but did mostly not become negative. This suggests an enduring synthesis of GAD-abs. Serial MR imaging suggests continuous, in part spreading, disease activity, however no destructive course.

A number of previous case reports or small patient series on therapy outcome of GAD-TLE using immunotherapy produced inconsistent results [3,4,30–35]. In a recently published study regarding seizure outcome of patients with autoimmune epilepsies, four GAD-TLE patients were included: two of them had a favourable outcome under immunotherapy with IVIG and MP gaining seizure-freedom for a period of 6–18 months [36]. Lilleker et al. [33] reported poor response on MP (*N* = 4) and IVIG (*N* = 1) in five patients with GAD-TLE.

Our poor therapeutic results even with strongly ab reducing measures such as apheresis challenge the direct pathogenicity of GAD-abs, which is still matter of debate [3,37–39]. There is evidence from *in vivo* studies of direct effects of GAD-ab containing biomaterials on neuronal tissues and in experimental animals [10,40]. A recent study showed reduced cortical GABA levels in MRI-spectroscopy in patients with GAD-TLE. The authors could, however, not determine whether their effects were due to a direct involvement of GAD-abs in pathogenesis or only epiphenomena of underlying unknown processes. They concluded that a clear response to immunotherapy would help to solve this particular question [41]. A major argument against direct involvement in pathological processes is the intracellular location of GAD with poor accessibility for abs. Recent findings on immunopathology of ab-associated encephalitides with three patients with GAD-TLE included support the hypothesis of a T-cell mediated immunopathology in these patients rather than humoral immune response [12]. The poor effect of apheresis therapies with priority on ab elimination in our study strengthens the assumption that these abs are not directly pathogenic.

According to histopathological findings [12], natalizumab was used as a promising new approach to block T-cell entry into the CNS. Although we observed encouraging therapy results in one patient, it has to be mentioned that the updated risk warnings for PML in patients with previous immunotherapy [28] are a hurdle for long-term off-label use in GAD-TLE patients at the moment. Future attempts with other biologicals directed to T-cells may overcome this. One option might be rituximab, which is now increasingly used in neurology and has an indirect inhibiting effect on pathogenic T-cells [38].

However, it should also be taken into account that extensive immunotherapies can cause severe side effects and their particular high costs, especially that of immunoadsorption and the newer immunosuppressants, put a strain on public health care systems. Hence, their use should be considered reasonably. Best therapeutic response in our cohort was achieved with corticosteroids, which are low-priced but have, on the other hand, severe side effects on long-term use.

Experiences in epilepsy surgery in GAD-TLE are rare and the small number of operated patients in our study group does not allow general conclusions but some interesting observations have to be emphasized. Two of the three operated GAD-TLE patients had relevant seizure frequency reduction under subsequent supportive immunosuppressive therapy but none of them remained seizure free after surgery. On the other hand, one operated patient experienced inflammatory relapse in contralateral mediotemporal structures after discontinuation of immunosuppressive therapy and did not regain previous cognitive level and seizure freedom after re-initiation of immunotherapy. The lack of seizure-free patients after surgery and extensions of encephalitic MRI features to the contralateral mediotemporal structures reflect the chronic and potentially progressive nature of this condition. Again, the fact that none of the patients newly developed hippocampal atrophy reflects a mild destructive potential. According to these findings, identification of GAD-TLE prior to surgery could be relevant for outcome prediction.

The fact that one patient newly developed insulin dependent diabetes mellitus and stiff-person-syndrome during follow up period raised the question wether the syndrome of GAD-TLE reflects only an aspect of a more generalized or multifocal GAD-ab-associated autoimmune syndrome. Consecutive long-term follow up of the patients could uncover such mechanisms.

There are, of course, relevant limitations to our study. We only considered patients from a tertiary epilepsy centre with chronic epilepsies. Our data are thus presumably biased towards more chronic and difficult-to-treat epilepsies. It cannot be excluded that

the patients harboured other abs in addition to GAD65 abs. This has been observed e.g. in Anti-GABA$_B$ receptor encephalitis [42,43]. However, overlaps seem not to be so frequent and do not necessarily mean that the prognosis is different (as has been reported with GAD-ab associated cerebellar ataxia and abs to the glycine receptor [44]). The patient group is larger than in most existing series, the numbers are, however, still small. Inclusion period ends in 2010, therefore we cannot exclude that newer treatment approaches could be more promising, although we are not aware of new systematic therapeutic efforts on this topic. Most patients received several interventions at different time points. Therefore, the evaluation of the individual therapies could not be done chronologically and the outcome variables are not independent. AED treatment was conducted in all patients, changes in medication occurred and influences on outcome cannot be excluded (however, it is likely that a more restricted handling of the AEDs would not have *improved* seizure outcome). Taken together, our data cannot go beyond a descriptive level. For further exploration and to share experience of this rare syndrome, a multicentric database could be helpful.

Despite these limitations, this is the first study which attempts to summarize the effect of various therapeutic interventions in a medium-sized sample of GAD-TLE patients. There were no resounding successes as are often observed with limbic encephalitis with abs against surface antigens. GAD-TLE seems to take a chronic course, resistant mostly to AED, immunotherapy and epilepsy surgery.

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Conflict of interest statement

MPM received payments for lecture and manuscript preparation from EISAI and UCB Pharma. CEE received honoraria for consultancy, expert testimony and lectures from UCB Pharma, EISAI, Desitin and Pfizer. He is employee of the Life and Brain Institute Bonn. CH was funded by grants from the Transregional Collaborative Research Centre SFB/TR3 A1, Bundesministerium für Bildung und Forschung and Deutsche Forschungsgemeinschaft, he received payments for board membership, consultancy, lectures, manuscript preparation and royalties from UCB Pharma, Desitin, VIAMED GmbH, EISAI, Glaxo Smith Kline. CGB gave scientific advice to Eisai (Frankfurt, Germany) and UCB (Monheim, Germany), undertook industry-funded travel with support of Eisai (Frankfurt, Germany), UCB (Monheim, Germany), Desitin (Hamburg, Germany), and Grifols (Frankfurt, Germany), obtained honoraria for speaking engagements from Eisai (Frankfurt, Germany), UCB (Monheim, Germany), Desitin (Hamburg, Germany), diamed (Köln, Germany), Fresenius Medical Care (Bad Homburg, Germany), and received research support from Astellas Pharma (München, Germany), Octapharma (Langenfeld, Germany), diamed (Köln, Germany) and Fresenius Medical Care (Bad Homburg, Germany). His employer (Krankenhaus Mara, Bielefeld, Germany) runs a laboratory for the detection of auto-antibodies including those described in this study; external senders are charged for antibody diagnostics. RS has received speaker fees from Cyberonics, EISAI and Novartis and had a consultancy agreement with UCB. CF, HZ and HU report no conflicts of interest.

Acknowledgements

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