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Abbreviations

Abs:	antibodies
aCL:	anti-cardiolipin
ACTH:	adrenocorticotropic hormone
ADAM:	a disintegrin and metalloproteinase
AMPAR:	-amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid receptor
ASD(s):	antiseizure drug(s)
auto-Abs:	autoantibodies
BBB:	blood-brain-barrier
BZD:	benzodiazepines
Caspr2:	contactin-associated protein-2
CCL-5:	cytokine-C-C-motif ligand-5 = RANTES
CD:	cerebellar degeneration
CJD:	Creutzfeldt-Jakob disease
CNS:	central nervous system
CNTF:	ciliary neurotrophic factor
CSF:	cerebrospinal fluid
DM-1:	type-1 diabetes mellitus
DPP-X:	di-peptidyl-peptidase-X
DWI:	diffusion weighted imaging
EEG:	electroencephalogram
FLAIR:	fluid-attenuated inversion recovery
GABAB-R:	gamma-amino-butyric acid type-B receptor
GAD:	glutamic acid decarboxylase
GluR3:	glutamate receptor subtype 3
GlyR:	glycine receptor
HDAC:	histone-deacetylase
HE:	Hashimoto's encephalitis/encephalopathy
HT:	Hashimoto's thyroiditis
HSE:	herpes simplex encephalitis
IgG (A,M):	Immunoglobulin of the G (A,M) class
ICAM-1:	intercellular adhesion molecule-1
IL:	interleukin
IL-1Ra:	interleukin-1-receptor antagonist
IT:	immunomodulatory treatment
IVIG:	intravenous immunoglobulins
LE:	limbic encephalitis
LGI-1:	leucin-rich glioma-inactivated protein-1
MDR-1:	multidrug resistance protein-1 (=p-glycoprotein (p-GP)
mGluR5:	metabotropic glutamate receptor subtype-5
MIP-1α:	macrophage inflammatory protein-1-alpha
MRI:	magnetic resonance imaging
MS:	multiple sclerosis
mRS:	modified Rankin Scale
MS:	multiple sclerosis
mTLS:	mesial temporal lobe sclerosis
mTOR:	mammalian target of rapamycin
MyD88:	myeloid differentiation primary response protein 88
NGF:	nerve growth factor
NMDA-R:	N-Methyl-D-Aspartat-receptor
NMO:	neuromyelitis optica
OCB:	oligoclonal bands
PCR:	polymerase chain reaction
PE:	plasma exchange
PERM:	progressive encephalomyelitis with rigidity and myoclonus
PRE:	pharmacoresistant (focal) epilepsy
PRES:	posterior reversible encephalopathy syndrome
RANTES:	regulated on activation, normal T cell expressed and secreted
SE:	status epilepticus
SLE:	systemic lupus erythematodes
SOD:	(mangane) superoxide dismutase
SPS:	stiff-person syndrome
SREAT:	steroid-responsive encephalitis associated with autoimmune thyroiditis
TGF-ß:	transforming growth factor-ß
TNF-α:	tumor necrosis factor-α
VGKC:	voltage-gated potassium channels

Summary

The influence of the immune system on the course und outcome of seizures and epilepsy has increasingly gained attention during the last two decades. The immune system and the nervous system are closely interconnected and alterations of one system may influence the other as well. For example, seizures may change cytokine production and cytokines may lower seizure threshold. Regarding autoimmunity and epilepsy, there are four different constellations to consider: (i) cellular

or humoral autoimmune responses cause a particular epilepsy syndrome (like Rasmussens's encephalitis), (ii) autoimmune diseases, both systemic and those confined to the central nervous system, are associated with seizures and epilepsy (like systemic lupus erythematosus), (iii) epileptic and syndromic disorders manifesting with seizures/epilepsy are associated with (antineuronal) auto-antibodies (like paraneoplastic and non-paraneoplastic limbic encephalitis, and (iv) epileptic syndromes without yet known associated autoimmune phenomena (like auto-Abs) respond to immunomodulatory therapies (like infantile spasms). This review aims at briefly discussing the basic autoimmune mechanisms involved in epileptogenesis, and then at presenting the main autoimmune epileptic disorders, especially the evolving group of different types of limbic encephalitis associated with various recently discovered antineuronal auto-antibodies.

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Key words: Autoimmunity, limbic encephalitis, antineuronal antibodies, pharmacoresistant epilepsy, immunomodulatory therapy

Autoimmunität und Epilepsien bei Erwachsenen

Der Einfluss des Immunsystems auf epileptische Anfälle und den Verlauf sowie die Behandelbarkeit und Prognose einer Epilepsie ist in den letzten beiden Jahrzehnten zunehmend in den Fokus der Aufmerksamkeit getreten. Das Nervensystem und das Immunsystem sind beide eng miteinander verbunden und beide können sich so stark gegenseitig beeinflussen. Veränderungen im einen System zeitigen meist auch solche im anderen. Zum Beispiel können epileptische Anfälle die Produktion von Cytokinen verändern, und diese wiederum können das Auftreten von Anfällen begünstigen. Auf Erkrankungen bezogen gibt es grundsätzlich vier Situationen von Autoimmunität bei Epilepsie zu betrachten: (i) eine zelluläre oder humorale Immunreaktion verursacht ein ganz bestimmtes Epilepsiesyndrom (zum Beispiel Rasmussen-Enzephalitis), (ii) Autoimmunerkrankungen, ob systemisch oder auf das Zentralnervensystem begrenzt, sind assoziiert mit epileptischen Anfällen oder Epilepsie (zum Beispiel systemischer Lupus erythematodes), (iii) epileptische und systemische Erkrankungen, die sich mit Anfällen/Epilepsie manifestieren, sind assoziiert mit anti-neuronalen auto-Antikörpern (zum Beispiel paraneoplastische und nicht-paraneoplastische limbische Enzephalitis), und (iv) epileptische Syndrome ohne bisher bekannten Zusammenhang mit dem Immunsystem sprechen auf eine Therapie mit immunmodulatorischen Medikamenten an (zum Beispiel West-Syndrom). Diese Übersichtsarbeit hat das Ziel, kurz die bei epileptischen Anfällen und Epilepsie grundlegenden Mechanismen der Autoimmunität zu erläutern und danach die wichtigsten autoimmunen epileptischen Syndrome des Erwachsenen vorzustellen, vor allem die verschiedenen Arten der limbischen Enzephalitiden mit den dazugehörigen, erst in den letzten Jahren entdeckten Autoantikörpern.

Schlüsselwörter: Autoimmunität, limbische Enzephalitis, antineuronale Antikörper, pharmakoresistente Epilepsie, immunmodulatorische Therapie

Auto-immunité et épilepsies chez l'adulte

L'influence qu'exerce le système immunitaire sur les crises d'épilepsie et sur l'évolution d'une épilepsie ainsi que sur les possibilités de traitement et le pronostic fait l'objet d'une attention particulière depuis ces deux dernières décennies. Le système nerveux et le système immunitaire sont étroitement liés, chacun pouvant donc fortement influencer l'autre. Des changements dans un système en entraînent généralement aussi dans l'autre. Des crises d'épilepsie peuvent par exemple modifier la production de cytokines, lesquelles, à leur tour, peuvent favoriser la survenue de crises. Sur le plan pathologique, quatre situations d'auto-immunité doivent être en principe prises en compte pour l'épilepsie : (i) une réaction immunitaire cellulaire ou humorale provoque un syndrome épileptique bien particulier (encéphalite de Rasmussen par exemple), (ii) les maladies auto-immunes, qu'elles soient systémiques ou limitées au système nerveux central, sont associées à des crises d'épilepsie ou à une épilepsie (lupus érythémateux disséminé par exemple), (iii) les maladies épileptiques et systémiques qui se manifestent par des crises / une épilepsie, sont associées à des auto-anticorps antineuronaux (encéphalite limbique paranéoplasique et non paranéoplasique par exemple), et (iv) les syndromes épileptiques sans lien connu à ce jour avec le système immunitaire répondent à un traitement immunomodulateur (syndrome de West par exemple). Ce travail récapitulatif a pour objectif d'expliquer brièvement les mécanismes d'auto-immunité à la base des crises d'épilepsie et de l'épilepsie, puis de présenter les principaux syndromes épileptiques auto-immuns de l'adulte, en particulier les différents types d'encéphalites limbiques avec les auto-anticorps associés découverts ces dernières années.

Mots clés : auto-immunité, encéphalite limbique, anticorps antineuronaux, épilepsie pharmaco-résistante, traitement immunomodulateur

Introduction

The immune system and the central nervous system (CNS) share more common ground than it might appear from first sight. Both are ubiquitous and essential for survival. They sense stimuli and react to them; these reactions can be immediate or delayed, episodic or sustained. Both form systems with high plasticity and harbor memory functions. And, last but not least, both systems are intimately and mutually interconnected.

The relationship between epilepsies and the immune system has gained attention only since about 20 years. During this period, however, there was an almost exponential increase in knowledge and publications, ignited by the dramatic improvements of lab and imaging technologies leading to the discovery of many (auto-)immune-mediated syndromes of patients with symptoms of limbic encephalitis (LE) and seizures etiologically not classifiable in previous times [1 - 4]. These encephalitides were initially thought to be exotic disorders, but some of them seem to be relatively common; for example, the LE associated with autoantibodies (auto-Abs) against the N-methyl-D-aspartate-receptor (NMDAR-) subtype 1A and -2/3 became the most incident encephalitis in patients younger than age 40 years in the California Encephalitis Project [5]. The knowledge of these disorders is not only important for diagnostic purposes, but it also enlarges the armamentarium of efficacious treatment options (i.e. immunomodulation) complex epileptic disorders beyond the use of antiseizure drugs (ASDs) usually prescribed for patients with epilepsy.

The present article aims at summarizing the current knowledge about the interplay between the immune system and seizures/epilepsies, and at presenting the most important autoimmune epileptic disorders focusing on the growing number of different types of limbic encephalitis which are associated with newly detected antineuronal antibodies (Abs).

The immune system in general can be divided into two functional units, the so called *innate* and the *adaptative* immune system (**Table 1**). While the innate immune system acts as an ubiquitous effective, but rather unspecific first-line defense against intruding agents (microbes and substances), the very flexible second-line adaptative immune system precisely targets a specific antigen, neutralizes and eliminates it. Both systems make use from immune mediators, the cytokines and chemokines. These compounds, like "immune hormones", regulate the activity, extent and localization of an immune response by systemic release and/or localization-related para- or autocrine secretion (**Table 2**).

Anatomically, the connections between the CNS and the immune system include the frontal premotor cortex, the anterior insula, the (mesial) temporal lobe, the hypothalamus, the pituitary gland and the brainstem [6]. Almost all of these structures also play an important role in seizures and epilepsy. The immune system of the brain, however, is particular with respect to the very protective and only selectively permeable blood-brain-barrier (BBB), to the high immune tolerance, the absence of a conventional lymphatic system and the usually very low turn-over of mono- and lymphocytes. Nevertheless, inflammatory reactions in response to infectious and autoimmune targets are frequent. If the process starts within the CNS, then the innate immune system is mainly involved, while the adaptative system is the dominant effector in the case of an external pathogen. Again, the transition of involvement from the innate to the adaptative immune system is modulated by cytokines and toll-like receptors [1, 7].

Alterations of integrity of the BBB play an important role in epileptogenesis. Extravasation of ictogenic plasma proteins, like cytokines and albumin, may provoke seizures. Thus, albumin seems to bind to the transforming growth factor-ß (TGF-ß)-receptor subsequently activating downstream pathways leading to hyperexcitability [8]. Leakage of the BBB also induces changes in protein expression of astrocytes, leading to astrocytic dysfunction with decreased buffering and re-uptake of glutamate from the synaptic cleft eventually resulting in excitotoxicity and seizures [9]. The opening of the BBB entails disturbed exchanges of ions, neurotransmitters and albumin; the intracellular raise of free calcium, glutamate, potassium, adenosine, and albumin, as well as a drop of magnesium increase the excitability of neurons and the risk of seizures [10]. The complex interplay of the immune system and epilepsy are summarized in the simplistic **Figure 1**.

Conversely, seizures also influence the immune system by changing cytokine levels, protein expression and the permeability of the BBB. All these factors are concisely reviewed by Li et al. [11] and summarized in **Table 3**. In general, pro-inflammatory, but also neuroprotective cytokines are intermittently up-regulated, followed by an increase in counter-regulatory cytokines. Nevertheless, an almost permanent low-intensity chronic inflammatory state accompanies difficult-to-treat epilepsies in animal models, and likely in humans too [3].

Autoimmune diseases and epilepsy in humans

Regarding autoimmunity and epilepsy, there are four different constellations to consider:

- *cellular or humoral autoimmune responses cause a particular epilepsy syndrome* (Rasmussens's encephalitis, Landau-Kleffner syndrome, continuous status epilepticus (SE) in slow-wave sleep)
- *autoimmune diseases, both systemic and those confined to the CNS, are associated with seizures and epilepsy* (multiple sclerosis (MS), systemic lupus erythematosus (SLE), celiac disease)
- *epileptic and syndromic disorders manifesting with*

Table 1: Synopsis of the innate and the adaptative immune system

	innate immune system	adaptative immune system
immune response	- based on the sensing of conserved pathogen or danger-associated molecular patterns (= "stored" immune memory) - immediate - rather unspecific - against external antigens	- based on previous recognition of pathogen or danger-associated molecular patterns (="acquired" immune memory) - delayed - highly specific - against external AND internal (=auto-!) antigens
main effector cells	phagocytosing cells: - granulocytes - monocytes/macrophages (in the CNS: microglia) - natural killer (NK-)cells	- regulatory (CD4+/CD25+) T-lymphocytes (tolerance vs. autoimmunity) - memory T-lymphocytes - cytotoxic (CD4+/CD8+) T-lymphocytes - antibody-producing B-lymphocytes
recognition	cell-to-cell contact by MHC-I/II-molecules toll-like receptors (TLRs)	pecific antigenic structures (epitopes) interactions with antigen-presenting cells (macrophages, dendritic cells, B-lymphocytes)
effector mechanisms	phagocytosis	direct cytotoxicity (NK-cells, cytotoxic T-lymphocyt.) antibody-dependent cellular cytotoxicity (ADCC) antibody coating/complement activation
mediators	cytokines	cytokines

Table 2: Essentials on cytokines

the most important components of the immune system beyond the immune cells

different types:
- lymphokines: e.g.: interleukins, interferons, TNF-α, TGF-β, etc.
- chemokines (« chemotactic » cytokines): e.g.: MIP, RANTES, PF-4, etc. (quarternary molecular structure fixed be cystein-disulfide-semicovalent bonds)
- growth-/stimulation factors: e.g.: granulocyte colony-stimulating factor (G-CSF), thrombospondin, etc.

produced by:
- lymphocytes
- monocytes/macrophages
- myeloic cells
- antigen-presenting cells
- neurons
- astrocytes
- microglia
- cells forming the blood-brain-barrier
- plexus choroideus

mode of action:
(auto-)/paracrine:
- release by cytokine-producing cells into the very close environment

endocrine:
- release by cytokine-producing cells into blood vessels, reaching close and remote target cells systemic effects (e.g. : IL-1β -> fever, TNF-α -> cachexia)

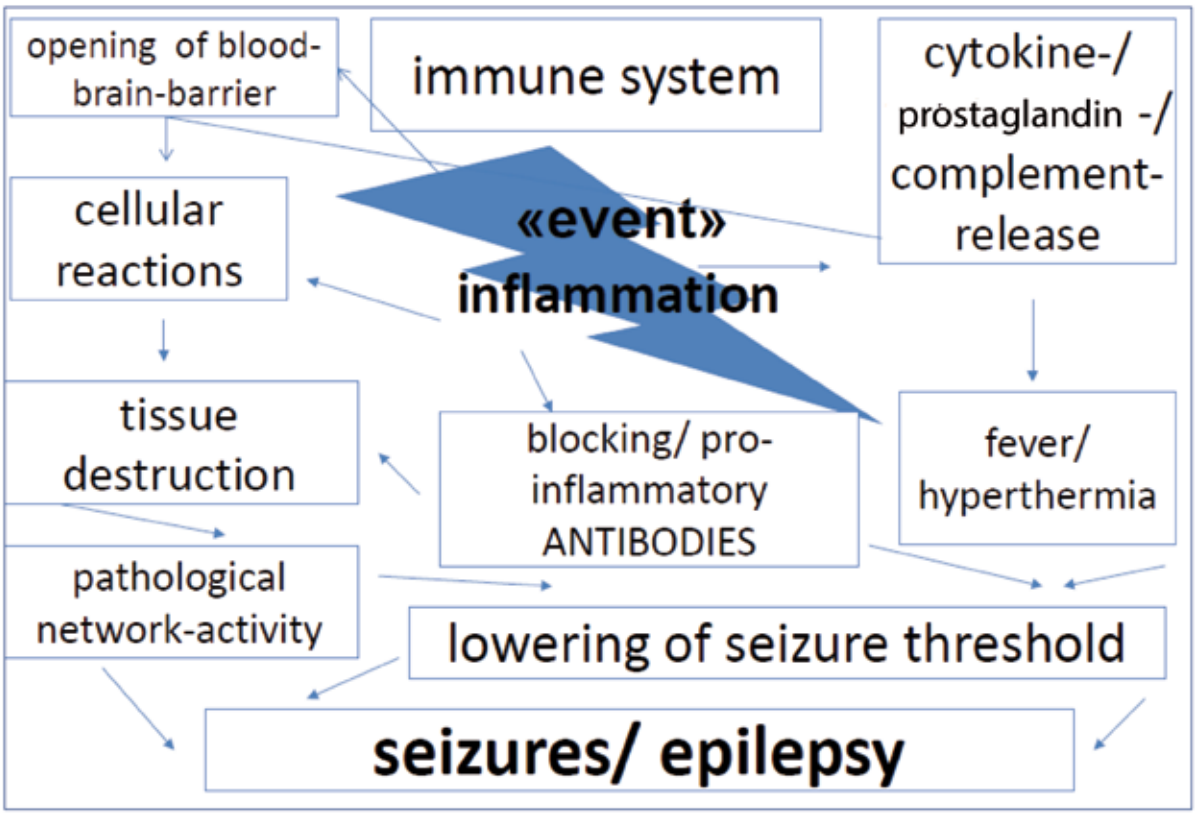

Figure 1: The complex interplay between the immune system and epilepsy

Table 3: Effects of seizures on the immune system [1, 11 - 13]

immune cells:
- higher proportion of monocytes and NK cells
- transient changes immediately after focal and generalized temporal lobe seizures, lasting for maximal 24 h [14]:

- increase :
  - total leukocyte count (+42%)
  - neutrophils (+55%)
  - lymphocytes (+45%)
  - NK cells (+104%)

- decrease :
  - CD4+-T-lymphocytes (-13% ; when under valproic acid : -23%)

cytokine release [15, 16]:
- in temporal lobe epilepsy: dependent on etiology, localization, and medications
- strongly pro-inflammatory and pro-convulsive cytokines:
- promote the destruction of GABAergic parvalbumin-positive inhibitory interneurons

- IL-6:
- cytokine expression and their receptors upregulated
- maximal increase after 6 h in patients with temporal lobe epilepsy [17]
- increase of > 50% up to 24 h after seizures in patients without mesial temporal lobe sclerosis [18]
- higher absolute levels in patients with right-sided seizure onset zone [18]
- markedly increased in handicapped persons and positively correlated with seizure frequency [19]
- may be elevated even interictally [20]

- IL-1β:
- cytokine expression and their receptors upregulated
- 100 x higher expression than IL-1Ra at inflammation onset
- higher absolute levels in patients under valproic acid [18]
- decreased levels during prolonged and repetitive seizures [21]
- cytotoxic: activation of inflammatory downstream pathways after binding to MyD88, a central regulator of activity of both the innate and the adapatative IM
- neuroprotective: by inducing nerve growth factor (NGF), cilliary neurotrophic factor (CNTF), insulin-like growth factor-1 (IGF-1), by stimulating antioxidative mechanisms (like increased expression of mangane superoxide dismutase (SOD)) and of calcium-binding proteins (like calbindin)

- TNF-α:
- cytokine expression and their receptors upregulated
- TNF-α-receptor activation influences expression of hippocampal glutamate receptors/excitability [22, 23]

- anticonvulsant and neuroprotective cytokine:
  - IL-1-receptor antagonist (IL-1Ra):
- production starts only hours after seizure and reaches equipoise levels to Il-1β (but not more)
- increased levels during prolonged and repetitive seizures [21]
- increased values in children with infantile spasms after treatment with adrenocorticotropic hormone (ACTH) and vigabatrine [24]
- use of synthetic IL-1Ra-agonists like Anakinra (Kineret®) decrease intensity and duration of seizures and SE in animal models [25]

seizures/epilepsy are associated with (antineuronal) auto-Abs (pharmacoresistant (focal) epilepsies (PRE), mesial temporal lobe sclerosis (mTLS)), (paraneoplastic and non-paraneoplastic) LE, type-1-diabetes mellitus (DM-1), anti-glutamate decarboxylase (-GAD-)auto-Abs associated syndromes, steroid-responsive encephalitis associated with autoimmune thyroiditis (SREAT))
- *epileptic syndromes without yet known associated autoimmune phenomena (like auto-Abs) respond to immunomodulatory therapies (infantile spasms)*

Cellular or humoral autoimmune responses causing a particular epilepsy syndrome

Since the three main entities (Rasmussen's encephalitis, Landau-Kleffner syndrome, and continuous status epilepticus (SE) in slow-wave sleep) of this group are autoimmune epilepsy syndromes mainly of childhood, they are covered in the article of C. Korff.

Systemic and CNS-restricted autoimmune diseases associated with seizures and epilepsy

Multiple sclerosis (MS)

Multiple sclerosis is a mainly demyelinating autoimmune disorder of the CNS; the specific pathogenic autoantibody could not be detected yet despite extensive research. The main pathogenic mechanisms seem to be T-lymphocyte-dependent, although the role of B-lymphocytes and plasma cells in the disease process receives increasing attention [26]. Similarly, the gray matter seems to be much more involved in the pathogenic mechanism of MS [27]. The latter is not unimportant when one looks at seizures in MS, as they are considered to involve mainly cortical structures and first studies point to a higher risk of seizures in MS patients with cortico-juxta-cortical inflammatory lesions [28, 29]. Overall, seizure incidence and epilepsy prevalence seem to be increased in patients with MS and the latter ranges between 0.5 - 19%, with a mean of 2.2% [30 - 34]. Seizures in patients with MS may occur at any stage of the disease; Rather rarely, it is an initial symptom, but then may present unpredictably and not clearly related to disease activity and acute inflammation (except for those patients with extensive cortical involvement). There is no evidence-based treatment for the seizures, but the patients respond well to ASDs. The choice of ASD is driven by their profile of interactions with the MS immunomodulatory treatment (IT) and of their adverse effects, of whom dizziness, ataxia, and cognitive impairment are especially important to avoid [35]. With regard to the ictogenic potential of current IT for MS, it might be interesting to observe seizure frequency of MS patients treated with the anti-integrin natalizumab which very efficiently tightens the BBB. Fabene et al. showed that compounds blocking leukocyte adhesion molecules resulted in prevention or abolition of seizures in different animal models [36]. Recent data indicates that glatiramer acetate may be protective for seizures although the exact mechanism is not known yet [37]. Conversely, the potassium channel blocking aminopyridines (3,4-aminopyridine, (dal-)fampridine) improving ambulation and alleviating fatigue not unexpectedly can lower the seizure threshold and should be used in patients with MS and known epilepsy with caution only, and especially overdose should be avoided [38].

Neuromyelitis optica (NMO)

There is only one report of a small number of Japanese patients with NMO (n=31) and seizures (n=4). The prevalence was higher than in MS with 12.9% and 6.7%, respectively. The patients with seizures and NMO had a significantly higher EDSS than those without seizures (7.6 vs. 5.5). Fortunately, the patients responded well to ASD treatment [39].

Systemic lupus erythematosus (SLE)

Systemic lupus erythematosus is a multifaceted, clinically very heterogeneously presenting severe autoimmune disorder. This is reflected by the diagnostic criteria which include 11 main features involving many organ systems, like skin, kidneys, oral cavity, joints, blood, and CNS where seizures are the principal manifestation [40]. Many auto-Abs may be present in patients with SLE [41]; on the CNS level, auto-Abs against subtypes of the glutamate receptor (mainly the α-amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid receptor-(AMPAR-) subtype GluR3 and the N-methyl-D-aspartate receptor (NMDAR) subtype NR2) were repeatedly reported and may explain the two main CNS affections occurring in SLE: seizures and psychosis. While the anti-GluR3-Abs are not cross-reacting with one of the main auto-Abs in SLE, i.e. double-stranded anti-DNA-Abs, the NR2-Abs do so and making it further plausible that seizures are a main feature of SLE [42]. The risk for seizures is about 3-4 times increased compared with the normal population and increases another 3.7 times when anti-cardiolipin-(aCL-)Abs are present. In larger SLE cohorts, the seizure incidence was about 12% [43 - 45]. Other risk factors for seizures include patients with strokes or TIA's due to vasculitis or thromboembolic disease, lupus nephritis, psychiatric symptoms [46]. While strokes and presence of aCL-Abs were associated with disease onset of SLE, renal manifestations, seizures at SLE onset and the persistence of aCL-Abs were associated with seizures during follow-up [44, 47]. About one

third of seizures occur before the definite diagnosis of SLE and are mainly generalized while seizures in the later course of the disease tend to be more focal [48]. Regarding treatment, valproic acid was effective in an animal model of SLE because of its antiapoptotic effect resulting from inhibition of histone-deacetylase; however, human experiences replicating this observation are lacking yet [49].

Celiac disease

Celiac disease was considered an autoimmune disorder of the gastrointestinal tract which results from the production of different auto-Abs against proteins of small intestine cells (transglutaminase and endomysium) leading to chronic lymphocytic inflammation and subsequently to a severe malabsorption syndrome of nutrition, vitamins and co-factors. This may lead to various (multi)organ deficiencies. However, the disorder is likely to be a multiorgan autoimmune disease which can involve also the brain (mainly manifesting with ataxia and seizures) or the peripheral nervous system (neuropathy), even in absence of gastrointestinal symptoms. It remains equivocal whether the CNS manifestations of celiac disease result from malabsorption (especially lipophilic vitamins A,D,E,K) or from a direct (likely cross-reactive) antineuronal and inflammatory mechanism [50]. The risk for seizures is essentially increased by 2-6 times, i.e., 1.1-5% of patients with celiac disease will experience them. Children are more frequently affected and then it may start even as SE [51 - 53]. Occipital lobe seizures are a clinical hallmark of epilepsy in celiac disease, even in adults [54]. More particular, there is a syndrome of celiac disease associated with marked bi-occipital calcifications and occipital seizures in patients with almost exclusively Italian descent [55]. Auto-Abs against transglutaminase isoform-6 have been found in these patients suggesting that an autoimmune mechanism is contributing to the process [56]. While vitamin-D deficiency is often present in patients with celiac disease, ectopic calcifications occur in a few of patients of Italian ancestry only; thus, a genetic alteration is likely responsible for this manifestation.

Epileptic and syndromic disorders manifesting with seizures/epilepsy associated with (antineuronal) auto-antibodies

auto-Abs-associated pharmacoresistant focal epilepsies (PRE)

The first significant step linking auto-Abs with epilepsy was the discovery of an auto-Ab against the subtype-3 of the glutamate receptor (GluR3) in Rasmussen's encephalitis, a very rare, severe inflammatory progressive epileptic encephalopathy of childhood [57]; although this antibody later was disproved to be the specific culprit, the report led to the introduction of immunomodulatory therapy (IT) in yet pharmacoresistant epileptic syndromes [58] and incited the intensive search for auto-antibodies in epilepsy in the last two decades [59 - 65]. All these studies are from single centre cohorts of pre-surgically evaluated patients with yet unexplained and pharmacoresistant epilepsy. In general, only a few patients (0 -16%) had one of these antineuronal auto-Abs and some authors suggested that their presence might be coincidental or that the high number of seizures in patients with PRE damaged the brain and the destruction of neurons might have facilitated exposition of neuronal antigens to the immune system which in turn reacts to them with the production of antineuronal auto-Abs. However, a recent study looking at the incidence of these auto-Abs in patients with new-onset or long lasting epilepsy found that the presence of auto-Abs was the same in both groups. Thus, the production of auto-Abs seems likely independent from duration of epilepsy. This data does not confirm the hypothesis that the auto-Abs result from presentation of damaged brain tissue antigens after frequent seizures [66]. Therefore, the clinical significance of antineuronal auto-Abs in patients with "epilepsy only" is not exactly known yet [2, 4, 67]. A very recent paper showed that a trial of IT improved seizure control in about 80% of patients after a single or combined IT, especially when the auto-Abs were located at the neuronal surface [68].

Mesial temporal lobe sclerosis (mTLS)

Mesial temporal sclerosis is an enigmatic, subacutely or chronically scaring of the mesial temporal structures of largely unknown origin very often leading to PRE. Immune processes have been implicated as a cause of mTLS since a long time, but the proof is still pending. The presence of human herpes virus-6-DNA in resected specimens of mTLS suggested that subacute or chronic low-intensity inflammation upon viral reactivation might contribute to the development of this pathology [69, 70]. Conversely, applying criteria for limbic encephalitis (LE), Bien et al. reported that this autoimmune syndrome was present in about a quarter of patients with mTLS referred for surgery [71]. A recent overview of Bauer et al. listed several rather unspecific inflammatory and immune phenomena (microglia-like cells with elevated IL-1ß- and p70S6-kinase expression (which activates mammalian target of rapamycin (mTOR)), increased expression of intercellular adhesion molecule-1 (ICAM-1) after downregulation of controlling microRNA's, and NFκB activation in reactive astrocytes) as contributors to mTLS [72].

Limbic encephalitis (LE)

Limbic encephalitis denotes a clinicopathological syndrome with auto-Abs-mediated paraneoplastic or non-paraneoplastic inflammation of neural tissue in the anatomical area of the limbic system (including the hippocampus, amygdala, anterior thalamic nuclei, septum, limbic cortex and fornix) [73]. The clinical hallmarks are subacutely or chronically progressing memory impairment, confusion, agitation or coma, seizures, psychosis, and may be accompanied by diffuse hyperintensities in the limbic system by MRI FLAIR sequences. While first thought to be an exclusively paraneoplastic disorder, the last decade lived the detection of many non-paraneoplastic forms of LE dependent on the antibodies involved. The main types of LE will be discussed next.

NMDAR-LE

The NMDAR-LE represents the best characterized autoimmune LE to date and deserves some extended presentation in the following.

The NMDARs are glutamate-gated cation (especially Ca^{2+}) channels, essential for synaptogenesis, use-dependent synaptic remodeling, and long-term plastic changes on the synaptic level. Overstimulation of the receptor leads to excitotoxicity and neuronal death. Plasticity changes upon receptor activation have been implicated into movement disorders, neuropathic pain, while blocking the receptors may lead to dementia and schizophrenia [74 - 76].

In 2005, a series of 7 patients with a subacute, treatment-responsive LE (4 associated with tumors and 3 not) was reported. Despite marked auto-Abs activity to hippocampus and cerebellum, auto-Abs against voltage-gated potassium channels (anti-VGKC-Abs) were detected in one patient only and the entity of the other patients remained obscured [77]. A few months later, the same researchers presented four women with an ovarian teratoma, suffering from LE associated with psychiatric symptoms and hypoventilation; three patients recovered after tumor removal and IT. The exact nature of the auto-Abs targeting hippocampal structures could not be elucidated [78]. Eventually, IgG auto-Abs to heterodimers of the NMDAR containing the subunits NR2A or NR2B in conjunction with the NR1A were verified as the cause of a paraneoplastic LE in 12 women with predominantly ovarian teratoma. Patients recovered after resection of the tumor and IT while not resected patients mainly died [79]. The special association of encephalitis and teratoma in young women led to the hypothesis that the disorder "acute juvenile female non-herpetic encephalitis" prevalent almost exclusively in Japan [80] might be the same or a very close disorder to NMDAR-encephalitis which was confirmed later [81]. Only one year after publication of the NMDAR results, a series of already 100 patients with NMDAR-LE was published, indicating an important incidence of the disease, especially in young women. The authors showed that 58% were paraneoplastic LE, but 42% had no detectable tumor. This paper also included the first 9 male patients and depicted the main and particular features (impaired consciousness (up to coma), behavioral alteration, psychosis, and seizures as early signs; orofacial and brachial dyskinesias, dysautonomia, and hypoventilation as later signs) of anti-NMDAR-LE (s. also **Table 4**), as well as data from CSF, MRI and EEG [82]. The group subsequently reported a series of 81 children and adolescents (< 18 years) pointing to the presence of the disorder also in this population. While these younger patients often had aphasia, movement disorders and seizures, they had less frequently tumors, hypoventilation and dysautonomia [83]. Pediatric dyskinetic encephalitis lethargica has been found to be a special manifestation of childhood NMDAR-LE [84]. Three pregnant patients (two with ovarian teratoma) with NMDAR-LE gave birth to two normal newborns (one pregnancy had to be terminated because of teratoma recurrence) and the mothers recovered well from LE [85]. Although NMDAR-LE mainly affects patients of younger age, a recent study showed that about 5% of patients may be older than age 45; these patients are more often males, have less frequently tumors, delayed diagnosis and treatment, and worse outcome when compared with the younger patients [86]. In 4% of patients, NMDAR-LE presents with isolated psychiatric episodes occuring in 80% during a NMDAR-LE relapse; this is important for the discussion of the impact of NMDAR-auto-Abs presence in psychiatric disorders [87]. NMDAR-LE may manifest with different combinations of main features, and absence of seizures, movement disorders, dysautonomia, and hypoventilation were reported [88]. Another patient presented with clinical and imaging features mimicking Rasmussen's encephalitis [89]. Detailed examination of movement disorders in children with NMDAR-LE revealed a large spectrum of manifestations and kids commonly present with more than one movement disorder [90]. The more cases are detected the more exotic features of NMDAR-LE are reported, like accompanying extensive myelitis [91], ophthalmoplegia and flaccid paraplegia [92], and exertional paroxysmal foot weakness [93] only to mention some examples.

The pathophysiology of NMDAR-LE has been increasingly elucidated. Ovarian teratomas as well as oocytes in normal ovaries express GluRs, the latter explaining why at least women without teratoma may develop anti-NMDAR-auto-Abs [79, 94, 95]. In order to cause NMDAR-LE, the binding of anti-NMDAR-Abs is dependent on amino acid identity of a small region within the GluN1 amino terminal domain [96]. A seminal study by Hughes et al. demonstrated that these auto-Abs cause a selective and reversible decrease in NMDAR surface density and synaptic localization by capping

Table 4: Human auto-antibodies (Abs) associated with seizures (and limbic encephalitides (LE))

auto-Abs	localization	paraneoplastic	seizures	neurological disorder(s)	main clinical features
neuronal					
anti-Hu	intracellular	yes (lung)	yes	limbic encephalitis/peripheral neuropathy/CD brainstem encephalitis	memory loss, confusion, coma, agitation, psychosis, cerebellar ataxia, dysautonomia. EPC
anti-Ma1/2	intracellular	yes (testicle)	yes	limbic encephalitis, brainstem encephalitis	memory loss, confusion, coma, agitation, psychosis, sleepiness, narcolepsy/cataplexy, eye movement disorders (vertical gaze palsy, ophthalomoplegia)
anti-CV2/CRMP5	intracellular	yes (lung/thymoma)	yes	limbic encephalitis, brainstem encephalitis	memory loss, confusion, coma, agitation, psychosis, cerebellar ataxia, chorea, uveo-retinal symptoms, myasthenic syndromes
anti-GAD	intracellular	rarely	yes	limbic encephalitis/CD/SPS/psychosis	memory loss, confusion,coma, agitation, psychosis, cerebellar ataxia, axial stiffness, hyperekplexia
anti-NMDAR	membranous	often (teratoma)	yes	limbic encephalitis	memory loss, confusion, coma, agitation, psychosis, seizures, status epilepticus, orofacial dyskinesias, dysautonomia, hypoventilation
anti-$GABA_BR$	membranous	often (lung)	yes	limbic encephalitis	seizures, status epilepticus, memory loss, confusion, coma, agitation, psychosis, cerebellar ataxia, opsoclonus/myoclonus syndrome
anti-AMPAR	membranous	often (lung/breast)	yes	limbic encephalitis	seizures, memory loss, confusion, coma, agitation, psychosis, rapidly progressive dementia
anti-gAchR	membranous	often (various)	rare	dysautonomia/PNP/encephalopathy	dysautonomia, memory loss, confusion, agitation
anti-VGKC	membranous	rarely (thymoma)	yes	limbic encephalitis/neuromytonia/PNP/Morv .yndrome	memory loss, confusion, coma, agitation, psychosis, hypersomnia, hyponatremia, myoclonus, dayautonomia, neuromyotonia
anti-LGI-1	membranous	rarely (thymoma)	yes (FDS)	limbic encephalitis/(PNP/neuromyotonia)	facio-brachial dystonic seizures preceding memory loss, confusion, coma, agitation, psychosis, neuromyotonia (rarely)
anti-Caspr2	membranous	rarely (thymoma)	yes	neuromyotonia/Morvan syndrome/PNP/limbic encephalitis brainstem encephalitis	neuromyotonia, hypersomnia, seizures, memory loss, confusion, coma, agitation, dementia
anti-DPPX	membranous	none	yes	limbic encephalitis & diarrhea	diarrhea preceding memory loss, confusion, agitation, coma, psychosis
anti-glycine	membranous	yes (lung)	rare	PERM	progressive confusion, coma, myoclonus, axial rigidity
anti-mGluR5	membranous	yes (Hodgkin lym.)	yes	Ophelia syndrome (limbic encephalitis & Hodgkin lymphoma)	memory loss, dementia, confusion,coma, agitation, psychosis, lymphoma
non-neuronal:					
anti-TPO	membranous	none	rare	SREAT ("Hashimoto encephalitis")	memory loss, confusion,coma, agitation, psychosis, seizures, status epilepticus, myoclonus, tremor, migraine, stroke-like episodes
anti-VGCC	membranous	yes (lung)	rare	Lambert-Eaton syndrome	proximal/axial myasthenic syndrome, confusion
ANA	intracellular	none	rare	connective tissue disorders/vasculitis	seizures
aCL	intracellular	partly	often	systemic lupus erythematosus/antiphospholipid syndrome	seizures
RF	intracellular	none	rare	connective tissue disorders/vasculitis	(seizures)
SS-A/SS-B	intracellular	none	rare	Sjögren's syndrome	(seizures)

Abbreviations: aCL: anti-Cardiolipin; AMPAR: α-amino-3-hydroxy-5-methyl-4- isoxazolepropionic acid receptor; ANA: antinuclear antibodies; Caspr2: contactin-associated protein-2; CD: cerebellar degeneration; CRMP5: collapsing-responsive membrane protein-5; DPPX: dipeptidyl-peptidase-X; EPC: epilepsia partialis continua; FDS: facio-brachial dystonic seizures; $GABA_BR$: γ-aminobutyric acid receptor type B; gAchR: ganglionic acetylcholine

through the whole auto-Abs (Fab and Fc-fragment) and disrupting the cross-talk with the Ephrin-B2-receptor at the membrane scaffold [97, 98]. This induces decreased synaptic currents without altering AMPAR-mediated currents. These effects could be replicated by infusing the auto-Abs into healthy rats [97]. Using a pre-conditioning paradigm with high-frequency stimulation over the prefrontal area, the transfer of anti-NMDAR-auto-Abs into the CSF led to a state of corticomotor hyperexcitability suggesting that the hypermotor symptoms of NMDAR-LE are related to the auto-Abs [99].

Seizures are an early clinical hallmark of NMDAR-LE, and many different EEG patterns may be observed. It has been recognized that rhythmic generalized delta-activity is often present in patients with LE [100]. The persistence of this rhythmic delta-activity correlating with marked impairment of cognition and consciousness may often represent prolonged non-convulsive SE [101 - 103], and it has been proposed that LE may represent limbic SE [104]. However, the most spectacular EEG finding was the observation of the combination of rhythmic delta-activity with superimposed high-frequency activity in the beta-band (**Figure 2**). This pattern was named "extreme delta brush" and was associated with prolonged hospitalization, longer duration of EEG-monitoring, and a trend towards worse outcome [105]. In children, a four stage pattern of EEG evolution during NMDAR-LE was recently reported: stage 1 showing normal background activity with some intermixed slow waves. Rhythmic unresponsive theta- or delta activity dominates stage 2 when the LE is at its maximum. Stage 3 in recovery displays a decrease of the rhythmic activity and reappearance of the occipital reactive background activity. EEG normalizes after 2 to 5 months (stage 4) [106].

Testing for serum anti-NMDAR-Abs in women under age of 45 with unexplained new-onset epilepsy may be helpful, especially when accompanied by psychiatric symptoms [107]. Although testing of the Abs in the CSF is not absolutely mandatory and presence of the anti-NMDAR-Abs in the serum is often sufficient for diagnosis [4, 108], CSF examination in patients with features suggesting anti-NMDAR-LE may be helpful and yields a sensitivity of 100% vs. 85.6 % in serum [109]. The presence of oligoclonal bands (OCB) in the CSF has a sensitivity and specificity of 34% and 96%, respectively. Compared to controls, the likelihood of the presence OCB is 8.5 times increased in patients with NMDAR-LE [110]. Abundant plasma cells in the brain of patients with NMDAR-LE may explain the presence of OCBs and anti-NMDAR-Abs in the CSF; in contrast, these Abs do not activate complement and may thus be the rationale why signs of inflammation (like contrast enhancement on MRI) are often absent in NMDAR-LE [111]. Anti-NMDAR-Abs in the CSF may persist for more than 15 years [112]. Recent retrospective data of a cohort of 250 NMDAR-LE and 100 controls suggests that higher serum and CSF titers were associated with teratoma and worse outcome. Titer changes in repeated CSF examinations more accurately reflected disease relapse than those observed in serum [109].

Imaging for NMDAR-LE can be useful; fluid-attenuated inversion recovery (FLAIR) sequences may show hyperintense signals in the limbic system and thereby support a diagnosis of LE. Diffusion-weighted imaging (DWI) sometimes displays vasogenic edema indicating inflammatory extravasation, and some parts of the limbic system can exhibit contrast enhancement. However, it is important to note that the MRI is normal in about 50% of cases with NMDAR-L; thus, a normal MRI

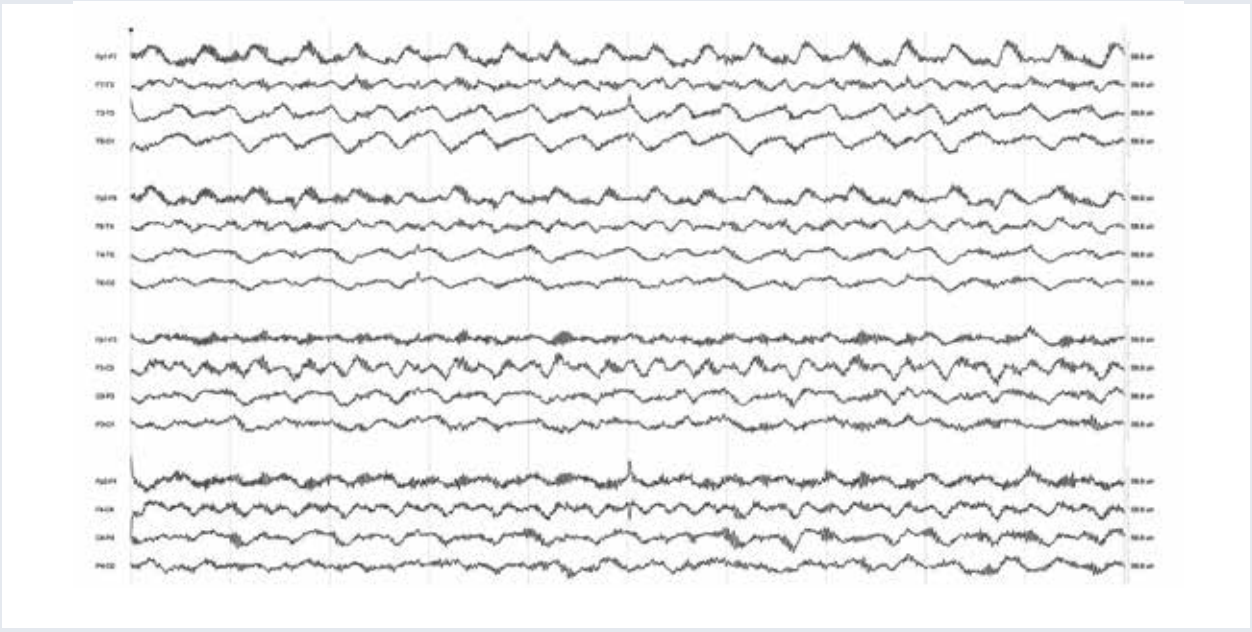

Figure 2: Continuous EEG-recording in a 19-year-old man with anti-NMDA receptor encephalitis associated with dyskinesias, seizures and coma (reprinted from Schmitt et al. [105], with permission from Neurology®)

will never preclude the presence of NMDAR-LE. Again, the mechanistic, essentially non-inflammatory incapacitation of the NMDAR is responsible for the often minor or absent changes in imaging methods which rely on inflammatory processes and BBB disruption [4, 97, 108]. Coupling of metabolic and imaging features by fluorodeoxyglucose-positron emission tomography reveals a disease-typical fronto-occipital activity gradient with hypermetabolism in the frontal lobes melting into hypometabolism in the occipital lobes. The extent of these changes was closely correlated with disease severity [99, 100].

The largest yet published cohort of patients followed up to 24 and more months included 577 patients (37% children) and their clinical and paraclinical features [115]. Response to treatment and outcome could be assessed in 501 patients. First-line treatment yielded improvement in 53% of patients and 57% of the non-responders received second-line therapy which resulted in better outcome than in the untreated patients. During the initial 24 months, a good outcome, as measured by a modified Rankin Scale (mRS) of 0 - 2, was observed in 78% after a median of 6 months; 6% died. Patients continued improving until 18 months after disease onset. At 24 months of follow-up, 81% of the patients still tracked had a good outcome. Factors highly significantly ($p < .0001$) associated with good outcome were early begin of treatment and no admission to intensive care unit. One or multiple relapses occurred in 9% of patients what is in contrast to an earlier small cohort where 24% of patients relapsed [116]. Two thirds of the relapses were significantly less severe than the initial episode, and often consisted in dominantly psychiatric manifestations. These observations were also valid for children of the cohort [115] and confirmed by two spectacular cases in a 5 year-old girl [117] and a 20 month-old boy [118], respectively. In contrast to adults, the long-term follow-up of 20 children revealed a disease onset with almost exclusively neurological symptoms (movement disorders, seizures and speech problems [119]. Mortality in this cohort was 5% and seems to share a relatively good prognosis similar to that of adults where 6% of patients died [115]. Additionally, a long-lasting course with refractoriness to therapy over 25 months has been reported [120]. Early removal or chemotherapeutic treatment of the tumor is essential for improvement in the patients with paraneoplastic NMDAR-LE [82, 115, 121]. During high disease activity, imaging can track brain atrophy which seems to be reversible upon treatment-associated improvement [122]. Rare cases of spontaneous recovery in patients with non-paraneoplastic NMDAR-LE are reported [123]. The movement disorders seen in NMDAR-LE seem to arise from dysfunction of the basal ganglia and not a primary epileptic phenomenon [82, 90]; however, when they do not respond to the basic IT, they may be difficult to treat. The vesicular mono-amino transporter protein blocker tetrabenazine and the inhalative narcotic isoflurane may be used in such cases [90, 124].

IgG-, IgA- and IgM-anti-NMDAR-Abs may also be present in both serum and CSF of patients with various other disorders, like in herpes simplex encephalitis (HSE) [125, 126] or rarely (about 0 - 2% in pathologically confirmed cases) in Creutzfeldt-Jakob disease (CJD) [127, 128]. The situation is further complicated as NMDAR-LE may mimic symptoms of CJD; if anti-NMDAR-Abs are not determined in patients with suspected (probable) CJD, they might die from a usually well treatable disease [128]. In the case of HSE, the presence of anti-NMDAR-Abs in these patients was explained by the massive CNS destruction freeing the NMDARs and inducing autoimmunity to them in some patients prone to develop intolerance [125]. However it could be also shown, that few patients may develop true NMDAR-LE after HSE, a clinical condition prior considered "HSV-PCR-negative relapsing HSE" [126]; thus, HSE may trigger the onset of NMDAR-LE [129]. NMDAR-LE may be associated if not triggered also by other autoimmune diseases, like Guillain-Barré syndrome [130].

While IgG anti-NMDAR-Abs cause classical NMDAR-LE, IgA anti-NMDAR-Abs were found in 29% of a small cohort of patients with progressive cognitive dysfunction; they are considered as a marker of synaptic immunity in slow cognitive impairment [131]. A heavily fuelled debate about the impact of anti-NMDAR-Abs present in psychiatric diseases started most recently. Anti-NMDAR-Abs were measured in a large cohort of patients with schizophrenia (n=121), major depression (n=70), bipolar disorder (n=38) and matched controls (n=230). While none of the controls harbored anti-NMDAR-Abs, they were present in almost 10% of schizophrenic patients. However, the Abs were of the IgA or IgM classes in these patients or not an IgG Abs directed against the LE-specific NMDAR subtype 1a (NR1a). Interestingly, 2 patients with schizophrenia had anti-NR1a-Abs and had to be reclassified as NMDAR-LE [132]; isolated schizophrenic episodes in NMDAR-LE seem to be rare [87]. The most recent study in an even larger cohort of schizophrenic (n=1081), Parkinson's disease (n=263) and affective disorder (n=148) patients, and 1325 matched healthy controls showed an anti-NMDAR1-Abs prevalence of 10.5%, with no difference in seroprevalence, titer, in vitro functionality between patients and healthy controls [133]. These results were very surprising and contrasting to the Steiner et al. study [132], the more as the anti-NMDAR-Abs were determined by the same laboratory. The authors claim for a genetic disposition by a specific polymorphism in schizophrenic patients and disrupted BBB in the prior history of seropositive patients and controls. Authoritative reviews address the important questions what is the impact of anti-NMDAR-Abs in psychosis [134] and whether they might cause psychosis [135].

VGKC

Auto-Abs against voltage-gated potassium channels (VGKC) impair their function and lead according to their large distribution to various neurological signs and symptoms. Patients positive for anti-VGKC-Abs may have (in descending order of frequency) cognitive impairment, seizures, dysautonomia, hyponatremia, myoclonus, dyssomnia, peripheral nerve dysfunction (incl. neuromyotonia), extrapyramidal, and brainstem dysfunction and cranial nerve palsies [136]. Hypothermia may also be present [137] as well as marked sleep disturbancies [138]. The trias of anti-VGKC-Abs-LE, severe hypersomnia, and peripheral neuropathy or neuromyotonia constitutes the rare Morvan's syndrome [139]. Pharmacoresistant epilepsy associated with anti-VGKC has been described [62, 64, 140]. In children, anti-VGKC-Abs may present with LE and SE [141]. Tumors (mostly thymoma and carcinoma) are present in about 5-40% of patients. The protean signs of the disorder often lead to misdiagnosis of CJD in these patients [142]. Recent studies confirmed the earlier observations that levels > 500 pM/l were more likely to be associated with autoimmune neurological disease [143].

Limbic encephalitis associated by anti-VGKC-Abs was first described in 2004 in a series of patients with LE negative for the known paraneoplastic Abs [144]. It was later shown that despite selective binding of I^{125}-α dendrotoxin to VGKC channels, the anti-VGKC-Abs rarely bind directly to these channels, but to mainly two channel-associated proteins, leucin-rich, glioma-inactivated protein -1 (LGI-1) by its receptors ADAM22 and 23 [145]. At the same time, the findings of LGI-1 as target auf auto-Abs was confirmed and a second target protein closely linked to the VGKC, contactin-associated protein-2 (Caspr-2), was identified [146]. Patients with anti-LGI-1-Abs had higher titers of anti-VGKC-Abs and cortical manifestations (i.e. LE) than patients with anti-Caspr2-Abs who have mainly peripheral motor hyperexcitability (i.e. neuromyotonia), although this was not mutually exclusive [147]. An effective immunotherapy regimen for the treatment of VGKC-LE has been proposed [148]; interestingly, anti-VGKC-LE remitted without IT and only after administration of AEDs in one case [149].

LGI-1

The metastasis-suppressing LGI-1 protein, highly expressed in the human hippocampus, gained much attention after it was discovered that mutations in the gene are causing autosomal dominant partial epilepsy with auditory features (ADPEAF) [150]. Seizures are also one of the dominant symptoms of patients with anti-LGI-1-Abs as part of their LE with its cardinal symptoms and signs [145, 146, 151]. This type of LE could be replicated in a model of LGI-1-deficient mice [152]. It was additionally shown that a particular seizure disorder precedes the onset of LE in almost 80% of adult patients. Their semiology consists of short frequent, bursting, and often unilateral faciobrachial dystonic seizures. The patients later develop impaired consciousness and amnesia, as well as hyponatremia [153]. Evolving anti-LGI-1-Abs-LE should be suggested in patients with this seizure type with no other obvious etiology [154]. In the first prospective study assessing seizure frequency and phenotype as well as response to IT, the patients responded significantly better to IT than to AEDs, again underscoring the value of timely correct diagnosis [155]. Patients with anti-LGI-1-LE may also present with chorea [156]. On the synaptic level, anti-LGI-1-Abs neutralize the interaction of LGI-1 with its receptors ADAM22 and 23, and also reduce synaptic AMPA receptors [157]. Contrast enhancing MRI changes were detected in the basal ganglia of patients with faciobrachial seizures [158].

Caspr2

While anti-Caspr2-Abs were associated mainly with peripheral motor hyperexcitability [146], few patients will develop anti-Caspr2-LE. These patients have a broad variety of encephalitic symptoms typical for LE, but often additional brainstem involvement, cranial nerve palsies, peripheral neuropathy, and neuromyotonia [159]. This constellation seems to be rare and unlike in NMDAR-LE, serum levels of anti-Caspr2-Abs seem hardly to reflect the disease course [160].

GAD

The cytosolic enzyme glutamic acid decarboxylase (GAD) plays a crucial role in the regulation of excitability of nerve cells since it catalyzes the formation of the strongest inhibitory neurotransmitter γ-amino butyric acid (GABA) from the highly excitatory neurotransmitter glutamate in one step. While the 67 kD isoform (GAD_{67}) is constitutive, the 65 kD isoform (GAD_{65}) is highly inducible and provides higher GABA levels in the brain during seizures [161]. It is obvious that blocking auto-Abs directed against GAD (anti-GAD-Abs) cause with a state of hyperexcitability due to the excess glutamate and a lack of GABA. Cortical low GABA levels have been measured in patients with epilepsy and anti-GAD-Abs [162]. These Abs not only impair $GABA_AR$-, but also $GABA_BR$-mediated synaptic currents [163] and function of $GABA_AR$ [164]. They may also reduce the number of GABAergic neurons by cytotoxic cell lysis through activated CD_4^+-T-lymphocytes in a microglia-rich environment [165]. Intracerebral administration of IgG anti-GAD-Abs reduces many essential inhibitory neurophysiological parameters important for motor and sensory control of movements [166].

The spectrum of neurological syndromes associated with anti-GAD-Abs includes epilepsy, cerebellar degeneration (CD), and stiff-person-syndrome (SPS). In addition, the anti-GAD-Abs are highly prevalent (> 80%) in patients with insulin-dependent type-1 diabetes mellitus, although levels were lower (500-5000 U/l) than in neurological disease [167, 168]. Reduced GAD_{67} levels and anti-GAD-Abs have also been implicated into the mechanisms of psychosis [169 - 172]. Intrathecal synthesis of anti-GAD-Abs is highly concordant to serum levels in neurological disorders; thus, determination of CSF levels is not mandatory [168]. While patients with SPS exhibit very high (>30'000 U/l) and those with CD medium (10'000-30'000 U/l) levels, those with epilepsy and LE may vary from medium unto very high levels [59, 65, 173-178], also in children [179] and in patients with otherwise unexplained SE [180, 181]. Prevalence of anti-GAD-Abs range from 0.8 to 1.5% and 2.6 to 5.9% in cohorts of unselected epilepsy patients and controles, respectively [59, 65, 176], and may raise up to 22% in patients with uncontrolled seizures [177]. Titers may be independent from duration of epilepsy and they often reflect disease course inconsistently [65, 176]. After a few published single cases of anti-GAD-Abs-LE [182 - 185], Malter et al. described a form of non-paraneoplastic LE associated with anti-GAD-Abs in 17% of a cohort of patients with new-onset temporal lobe epilepsy and fulfilling the criteria for LE. Compared with the cohort of anti-VGKC-LE patients, those with anti-GAD-Abs were significantly younger and had more often oligoclonal bands in CSF. The anti-GAD-Abs titers in CSF remained highly elevated and none of the patients became seizure free despite intensive IT. Anti-GAD-Abs-LE seems to be a chronic and non-remitting disorder among the spectrum of non-paraneoplastic LE [186]. Rarely, the disorder may also affect young children with good response to IT [187]. Eventually, another type of anti-GAD-Abs-LE without epilepsy, but evolving into dementia and CD was reported in a 11 year-old girl [188].

AMPA

In 2009, Lai et al. reported a form of paraneoplastic, well-responsive LE associated with Abs against the GluR1 and GluR2 receptor subunits of the glutamatergic α-amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid receptor (AMPAR) highly abundant in hippocampus. Ninety percent of patients were women and 70% of patients had tumors of the lung, breast or thymus. Again 90% responded to IT and oncological treatment; however, LE tended to relapse without tumor recurrence, and to impair long-term outcome [189]. Further cases of anti-AMPAR-LE were described [190] and recently, the particular case of a pregnant woman with anti-AMPAR-LE rapidly developing extensive brain atrophy pointed to the possible larger sequelae of a formerly restricted inflammatory process in the limbic system [191].

$GABA_B$

Lancaster et al. presented 2010 a case series of 15 patients suffering from paraneoplastic (n=7, mainly lung cancer) or immune-mediated LE associated with auto-Abs against the B1-subunit of the heterodimeric $GABA_B$ receptor (anti-$GABA_B$R-Abs) with early and highly frequent seizures as the predominant symptom. Rigorous anticancer treatment and IT led to an improvement in 9 of 10 patients, while non-adherence to such therapies led to deterioration in the others. Determination of anti-$GABA_B$R-Abs in a control cohort (n=104) showed presence in 2 normal individuals [192]. The findings were replicated in a large case series of 70 patients with LE of whom 14% were associated with anti-$GABA_B$R-Abs. Interestingly, anti-$GABA_B$R-Abs could not be found in any of 77 patients with anti-GAD-Abs associated disorders, like LE, CD, epilepsy and stiff-person syndrome (SPS) [193]. Single cases with an enlarging clinical spectrum (paraneoplastic cerebellar ataxia [194] and brainstem encephalitis [195]) were subsequently observed. The most recent series of patients (n=20) with anti-$GABA_B$R-LE again found a similar paraneoplastic to non-paraneoplastic pattern with lung cancer being mainly associated with the disease. All except of one patient responded to intensive oncological and IT. Clinical manifestations beyond classical findings of LE included ataxia, inaugural SE, and opsoclonus-myoclonus syndrome [196]. In a large cohort study 7 of 3'989 (0.2%) patients suspected for autoimmune encephalopathy were positive for anti-$GABA_B$R-Abs. Five out of 49 patients (10%) with a before unclassified antineuronal IgG tested positive for anti-$GABA_B$R-Abs. About 1.3% (5 of 384) patients with at least one onconeuronal Ab typical for small-cell lung cancer had also anti-$GABA_B$R-Abs [197]. In this anti-$GABA_B$R-Abs-LE too, MRI imaging is often normal, but reversible functional abnormalities can be detected by SPECT. The hypoperfusion of the frontal, parietal, and medial temporal lobes, as well as the thalamus and cerebellum present during the acute phase normalizes upon IT and demonstrates the non-structural, but functional neurophysiological effect of auto-Abs in LE [198].

DPPX

The growing family of auto-Abs associated with LE was enlarged by the discovery of Abs against the neuronal cell surface antigen dipeptidyl-peptidyl-like protein-6 (anti-DPPX-Abs), a subunit of the voltage-gated potassium channel Kv4.2. Patients had symptoms typical for LE (seizures, agitation, confusion, myoclonus, tremor) and, very particular, severe prodromal diarrhea. The anti-DPPX-Abs heavily reacted with the Kv4.2. channels in the myenteric plexus. The course of the disease, especially the neuropsychiatric manifestations, was protracted and relapses occurred frequently after tapering IT [199].

Paraneoplastic encephalitic Abs not otherwise specified

In a large cohort (n=249) of predominantly (91%) young female patients with teratoma and paraneoplastic LE, 85% had anti-NMDAR-Abs, but 22/38 (58%) of the anit-NMDAR-Abs-negative patients had a particular and quite uniform type of LE with additionally frequent opsoclonus and prominent signs of brain stem encephalitis. The majority of patients (74%) responded very well to tumor removal and IT [200].

anti-α1-glycine receptor (anti-GlyR)

A rare neurological syndrome with progressive encephalomyelitis, rigidity and (stimulus-sensitive) myoclonus (PERM) was first reported in 1976 [201]. Later on, the autoimmune origin of the disease was discovered and it may be associated with a variety of different neuronal anti-Abs, like anti-Ri- [202], anti-Ma3, anti-GAD-, antiLGI-1-, [203], and especially anti-α1-glycine receptor-(anti-GlyR-Abs) [204 - 207], even in children. Seizures may exceptionally occur.

anti-mGluR5 (Ophelia)

The rare association of LE in patients with Hodgkin's lymphoma is called Ophelia syndrome because of the prominent progressive memory loss together with emaciation [208]. Recently, the presence of auto-Abs directed against the metabotropic glutamate receptor 5 (mGluR5), a receptor crucial for memory consolidation and learning in the hippocampus, was reported in the serum and the CSF patients with Ophelia syndrome [209, 210].

Steroid-responsive encephalitis associated with autoimmune thyroiditis (SREAT)

Autoimmune thyroiditis, mainly Hashimoto's thyroiditis (HT) and to a lesser extent Graves' disease, may be associated with seizures. While high thyroid hormone levels or thyroid receptor-stimulating auto-Abs may provoke thyrotoxicosis with mainly generalized tonic-clonic seizures [211] or exacerbate seizures in patients with epilepsy [212, 213], patients with HT and anti-thyroid peroxidase-Abs (anti-TPO-Abs) very rarely have seizures. However, a tiny proportion of the high number of patients with HT (about 10% of > 50-years-old women) develop a mysterious syndrome, Hashimoto's encephalitis [214 - 221] or steroid-responsive encephalitis with autoimmune thyroiditis (SREAT) [222]. The main features of the disorders are subacutely progressive behavioral changes and psychosis, impairment of consciousness, memory loss, seizures or SE, myoclonus, tremor, and stroke-like episodes. The diagnosis of HE is made by the clinical picture of a LE, seizures, and positive anti-TPO-Abs, and by exclusion of all other causes of infectious and inflammatory autoimmune encephalitis. It is important to note that between 30 and 50% of the patients are euthyroid and a normal TSH will not at all exclude SREAT. The EEG of these patients is almost always altered, 70 - 90% of patients have seizures and 10 - 20% even SE. Titers of anti-TPO-Abs only inconsistently reflect disease course, however, SREAT (nomen est omen!) extremely well responds to treatment with steroids: symptoms of patients and their EEG clear up within 2 - 4 weeks [218 - 223]. Despite the fundamental role of thyroid hormones for the well-functioning of the brain [224], the exact pathomechanism of SREAT, the anti-TPO-Abs, and the HT is not elucidated yet. It remains unresolved whether the anti-TPO-Abs are directly involved in the encephalitic process or only an innocent bystander. The latter has received broad acceptance since HE occurs so rarely despite the very high prevalence of anti-TPO-Abs.

Type 1 diabetes mellitus (DM-1)

Case reports pointed to an association of DM-1 and epilepsy [225, 226]. The prevalence of DM-1 in a large cohort (n=518) of young patients with genetic generalized epilepsies was unexpectedly high (odds ratio: 4.4 (2.1 - 9.2) [227]. Later findings yielded conflicting results as both confirmatory [228, 229] and contradictory [230] studies were reported [231]. Type 1 diabetes is an autoimmune disease associated with different auto-Abs against pancreatic structures, but also anti-GAD-Abs in serum and CSF [174]. Pancreatic GAD may play an important role in glucose homeostasis as activation of GABA-specific K^+-ATP-activated chloride channels regulate the early insulin response to glucose intake [232]. Thus, the anti-GAD-Abs might be the link between DM-1 and the high prevalence of (genetic generalized) epilepsy [233, 234]. While some authors reported the safety of the ketogenic diet in patients with epilepsy and DM-1 [235], others suggested an increased risk for diabetic ketoacidosis per se in DM-1 patients with epilepsy [236]. It is still not clear whether IT would improve seizure control in diabetic patients with epilepsy; of course, IT containing corticosteroid should be used with caution only.

Epileptic syndromes without yet known associated autoimmune phenomenons responding to immunomodulatory therapies

Infantile spasms (West syndrome)

Infantile spasms are an age-dependent severe epileptic syndrome emerging in infants under the age of 1 year and rarely lasting beyond age of 2 years. "Immune therapy" with corticosteroids or adrenocorticotropic hormone (ACTH) is one therapeutic mainstay despite the lack of evidence that the syndrome has an autoimmune origin [237]. This syndrome will be detailed in the article of Christian Korff.

Treatment considerations

This topic is covered by the article of Drs. Viaccoz and Lalive d'Epiney in this issue.

Perspectives

It is obvious that the next years will see the discovery of many other new antineuronal auto-Abs involved in inflammatory CNS disease. The improved awareness for autoimmune LE and increased test frequencies will help to better characterize the epidemiology and clinical features of these disorders, as well as making these tests faster available to a broader audience for a lower prize.

Future research will look at the more precise elucidation of the pathomechanisms of LE and how these antineuronal Abs are involved in the inflammatory process and neurological dysfunction at a molecular, neurophysiological and network level.

New and more specific treatments may help to improve outcome of the patients with autoimmune epilepsy und overcome refractoriness of seizures. Particularly, innovative therapeutics will target the yet difficult to treat types of LE associated with Abs directed against intracellular antigens and prevent relapse of LE.

While it is obvious that clearly delineated autoimmune syndromes associated with epilepsy should be treated with both IT and ASD, it remains unclear whether PREs associated with an antineuronal antibody, but lacking signs of LE should be treated with IT. Some single center experiences retrospectively addressing this question have been published and they suggest that IT may be a valuable tool to treat PRE associated with antineuronal Abs, but that additional prospective studies regarding the natural history of autoimmune PRE are warranted before broader use of IT can be recommended [68, 238, 239].

References

1. *Vezzani A, Granata T. Brain inflammation in epilepsy: experimental and clinical evidence. Epilepsia 2005; 46: 1724-1743*
2. *Vincent A, Irani SR, Lang B. The growing recognition of immunotherapy-responsive seizure disorders with autoantibodies to specific neuronal proteins. Curr Opin Neurol 2010; 23 : 144-150*
3. *Vezzani A, French J, Bartfai T, Baram TZ. The role of inflammation in epilepsy. Nat Rev Neurol 2011; 7: 31-40*
4. *Lancaster E, Dalmau J. Neuronal autoantigens – pathogenesis, associated disorders and antibody testing. Nat Rev Neurol 2012; 8: 380-390*
5. *Gable MS, Sheriff H, Dalmau J et al. The frequency of autoimmune N-methyl-D-aspartate receptor encephalitis surpasses that of individual viral etiologies in young individuals enrolled in the California Encephalitis Project. Clin Infect Dis 2012; 54: 899-904*
6. *Meisel C, Schwab JM, Prass K et al. Central nervous system injury-induced immune deficiency syndrome. Nat Rev Neurosci 2005; 6: 775-786*
7. *Vezzani A, Maroso M, Balosso S et al. IL-1 receptor/Toll-like receptor signaling in infection, inflammation, stress and neurodegeneration couples hyperexcitability and seizures. Brain Behav Immun 2011; 25: 1281-1289*
8. *Friedman A, Kaufer D, Heinemann U. Blood-brain barrier breakdown inducing astrocytic transformation: novel targets for the prevention of epilepsy. Epilepsy Res 2009; 85: 142-149*
9. *Marchi N, Angelov L, Masaryk T et al. Seizure-promoting effect of blood-brain barrier disruption. Epilepsia 2007; 48: 732-742*
10. *Janigro D. Are you in or out? Leukocyte, ion, and neurotransmitter permeability across the epileptic blood-brain barrier. Epilepsia 2012; 53(Suppl 1): S26-S34*
11. *Li G, Bauer S, Nowak M et al. Cytokines and epilepsy. Seizure 2011; 20: 249-256*
12. *Vezzani A, Balosso S, Ravizza T. The role of cytokines in the pathophysiology of epilepsy. Brain Behav Immun 2008; 22: 797-803*
13. *Ravizza T, Gagliardi B, Noé F et al. Innate and adaptative immunity during epileptogenesis and spontaneous seizures: evidence from experimental models and human temporal lobe epilepsy. Neurobiol Dis 2008; 29: 142-160*
14. *Bauer S, Köller M. Cepok S et al. NK and CD4+ T cell changes in blood after seizures in temporal lobe epilepsy. Exp Neurol 2008; 211: 370-377*
15. *Lehtimäki KA, Keränen T, Palmio J et al. Increased plasma levels of cytokines after seizures in localization-related epilepsy. Acta Neurol Scand 2007; 116: 226-230*
16. *Nowak M, Bauer S, Haag A et al. Interictal alterations of cytokines and leukocytes in patients with active epilepsy. Brain Behav Immun 2011; 25: 423-428*
17. *Alapirtti T, Rinta S, Hulkkonen J et al. Interleukin-6, interleukin-1 receptor antagonist and interleukin-1beta production in patients with focal epilepsy: video EEG study. J Neurol Sci 2009; 280: 94-97*
18. *Bauer S, Cepok S, Todorova-Rudolph A et al. Etiology and site of temporal lobe epilepsy influence postictal cytokine release. Epilepsy Res 2009; 86: 82-88*
19. *Lehtimäki KA, Liimatainen S, Petola J, Arvio M. The serum level of interleukin-6 in patients with intellectual disability and refractory epilepsy. Epilepsy Res 2011; 95: 184-187*
20. *Hulkkonen J, Koskkallio E, Rainesalo S et al. The balance of inhibitory and excitatory cytokines is differently regulated in vivo and in vitro among therapy resistant epilepsy patients. Epilepsy Res 2044; 59: 199-205*

21. *Lehtimäki KA, Keränen T, Palmio J, Peltola J. Levels of Il-1beta and Il-1ra in cerebrospinal fluid of human patients after single and prolonged seizures. Neuroimmunomodulation 2010; 17: 19-22*
22. *Baslosso S, Ravizza T, Pierucci M et al. Molecular and functional interactions between tumor necrosis factor-alpha receptors and the glutamatergic system in the mouse hippocampus: implications for seizure susceptibility. Neuroscience 2009; 161: 293-300*
23. *Riazi K, Galic MA, Kuzmiski JB et al. Microglial activation and TNFalpha production mediate altered CNS excitability following peripheral inflammation. Proc Natl Acad Sci USA 2008; 105: 17151-17156*
24. *Yamanaka G, Kawashima H, Oana S et al. Increased level of serum interleukin-1 receptor antagonist subsequent to resolution of clinical symptoms in patients with West syndrome. J Neurol Sci 2010; 298: 106-109*
25. *Marchi N, Fan Q, Ghosh C et al. Antagonism of peripheral inflammation reduces the severity of status epilepticus. Neurobiol Dis 2009; 33: 171-181*
26. *Disanto G, Morahan JM, Arnett MH et al. The evidence for a role of B cells in multiple sclerosis. Neurology 2012; 78: 823-832*
27. *Calabrese M, Favaretto A, Martini V, Gallo P. Grey matter lesions in MS: from histology to clinical implications. Prion 2013; 7: 20-27*
28. *Calabrese M, De Stefano N, Atzori M et al. Extensive cortical inflammation is associated with epilepsy in multiple sclerosis. J Neurol 2008; 255: 581-586*
29. *Martinez-Lapiscina EH, Ayuso T, Lacruz F et al. Cortico-juxtacortical involvement increases risk of epileptic seizures in multiple sclerosis. Acta Neurol Scand 2013; 128: 24-31*
30. *Spatt J, Chaix R, Mamoli B. Epileptic and non-epileptic seizures in multiple sclerosis. J Neurol 2001; 248: 2-9*
31. *Sokic DV, Stojsavlievic N, Drulovic J et al. Seizures in multiple sclerosis. Epilepsia 2001; 42: 72-79*
32. *Poser CM, Brinar VV. Epilepsy and multiple sclerosis. Epilepsy Behav 2003; 4: 6-12*
33. *Koch M, Uyttenboogaart M, Polman S, De Keyser J. Seizures in multiple sclerosis. Epilepsia 2008; 49: 948-953*
34. *Kelley BJ, Rodriguez M. Seizures in patients with multiple sclerosis: epidemiology, pathophysiology and management. CNS Drugs 2009; 23: 805-815*
35. *Koch MW, Polman SK, Uyttenboogaart M, De Keyser J. Treatment of seizures in multiple sclerosis. Cochrane Database Syst Rev 2009. Jul 8; (3):CD007150. Doi:10.1002/14651858*
36. *Fabene P, Navarro Mora G, Martinello M et al. A role for leukocyte-endothelial adhesion mechanisms in epilepsy. Nat Med 2008; 14: 1377-1383*
37. *You Y, Zhao Y, Bai H et al. Glatiramer acetate, an anti-demyelination drug reduced rats' epileptic seizures induced by pentylentetrazol via protection of myelin sheath. Eur J Pharm Sci 2013; 49: 366-370*
38. *Cornblath DR, Bienen EJ, Blight AR. The safety profile of dalfampridine extended release in multiple sclerosis clinical trials. Clin Ther 2012; 34: 1056-1069*
39. *Nakano H, Tanaka M, Kinoshita M et al. Epileptic seizures in Japanese patients with multiple sclerosis and neuromyelitis optica. Epilepsy Res 2013; 104: 175-180*
40. *Hochberg MC. Updating the American College of Rheumatology revised criteria for the classification of systemic lupus erythematosus. Arthritis Rheum 1997; 40: 1765*
41. *Rahman A, Isenberg DA Systemic lupus erythematosus. N Engl J Med 2008; 358: 929-939*
42. *Levite M, Ganor Y. Autoantibodies to glutamate receptors can damage the brain in epilepsy, systemic lupus erythematosus and encephalitis. Expert Rev Neurother 2008; 8: 1141-1160*
43. *Liou HH, Wang CR, Chen CJ et al. Elevated levels of anticardiolipin antibodies and epilepsy in lupus patients. Lupus 1996; 5: 307-312*
44. *Appenzeller S, Cendes F, Costallat LT. Epileptic seizures in systemic lupus erythematosus. Neurology 2004; 63: 1808-1812*
45. *Padovan M, Castellino G, Bortoluzzi A et al. Factors and comorbidities associated with central nervous system involvement in systemic lupus erythematosus: a retrospective cross-sectional case-control study from a single center. Rheumatol Int 2012; 32: 129-135*
46. *Greenberg BM. The neurologic manifestations of systemic lupus erythematosus. Neurologist 2009; 15: 115-121*
47. *Mikdashi J, Krumholz A, Handwerger B. Factors at diagnosis predict subsequent occurrence of seizures in systemic lupus erythematosus. Neurology 2005; 64: 2102-2107*
48. *Mackworth-Young CG, Hughes GR. Epilepsy: an early symptom of systemic lupus erythematosus. J Neurol Neurosurg Psychiatry 1985; 48: 185*
49. *Mishra N, Reilly CM, Brown DR et al. Histone deacetylase inhibitors modulate renal disease in the MRL-lpr/lpr mouse. J Clin Invest 2003; 111: 539-552*
50. *Hadjivassilliou M, Sanders DS, Grünewald RA et al. Gluten sensitivity: from gut to brain. Lancet Neurol 2010; 9: 318-330*
51. *Chapman RW, Laidlow JM, Colin-Jones D et al. Increased prevalence of epilepsy in coeliac disease. Br Med J 1978: 2: 250-251*
52. *Pengiran-Tengah DS, Holmes GK, Wills AJ. The prevalence of epilepsy in patients with celiac disease. Epilepsia 2004; 45: 1291-1293*
53. *Hijaz NM, Bracken JM, Chandratre SR. Celiac crisis presenting with status epilepticus and encephalopathy. Eur J Pediatr 2013; Jul 31st Epub ahead of print*
54. *Ambrosetto G, Antonini L, Tassinari CA. Occipital lobe seizures related to clinically asymptomatic celiac disease in adulthood. Epilepsia 1992; 33: 476-481*
55. *Gobbi G. Coeliac disease, epilepsy and cerebral calcifications. Brain Dev 2005; 27: 189-200*
56. *Johnson AM, Dale RC, Wienholt L et al. Coeliac disease, epilepsy, and cerebral calcifications: association with TG & antibodies. Dev Med Child Neurol 2013; 55: 90-93*
57. *Rogers SW, Andrews PI, Gahring LC et al. Autoantibodies to glutamate receptor GluR3 in Rasmussen's encephalitis. Science 1994; 265: 648-651*
58. *Andrews PI, Dichter MA, Berkovic SF et al. Plasmapheresis in Rasmussen's encephalitis. Neurology 1996; 46: 242-246*
59. *Kwan P, Sills GJ, Kelly K et al. Glutamic acid decarboxylase autoantibodies in controlled and uncontrolled epilepsy: a pilot study. Epilepsy Res 2000; 42: 191-195*
60. *Peltola J, Kulmala P, Isojärvi J et al. Autoantibodies to glutamic acid decarboxylase in patients with therapy-resistant epilepsy. Neurology 2000; 55: 46-50*
61. *Sokol DK, McIntyre JA, Wagenknecht DR et al. Antiphospholipid and glutamic acid decarboxylase antibodies in patients with focal epilepsy. Neurology 2004; 62: 517-518*
62. *McKnight K, Jiang Y, Hart Y et al. Serum antibodies in epilepsy and seizure-associated disorders. Neurology 2005; 65: 1730-1736*
63. *Vianello M, Keir G, Giometto B et al. Antigenic differences between neurological and diabetic patients with anti-glutamic acid decarboxylase antibodies. Eur J Neurol 2005; 12: 294-299*
64. *Majoie HJ, de Baets M, Renier W et al. Antibodies to voltage-gated potassium and calcium channels in epilepsy. Epilepsy Res 2006; 71: 135-141*

65. *Liimatainen S, Peltola M, Sabater L et al. Clinical significance of glutamic acid decarboxylase antibodies in patients with epilepsy. Epilepsia 2010; 51: 760-767*
66. *Brenner T, Sills GJ, Hart Y et al. Prevalence of neurologic autoantibodies in cohorts of patients with new and established epilepsy. Epilepsia 2013; 54: 1028-1035*
67. *Vincent A, Bien CG, Irani SR, Waters P. Autoantibodies associated with diseases of the CNS: new developments and future challenges. Lancet Neurol 2011; 10: 759-772*
68. *Toledano M, Britton JW, McKeon A et al. Utility of an immunotherapy trial in the evaluation of patients with presumed autoimmune epilepsy. Neurology 2014 (in press)*
69. *Donati D, Akhyani N, Fogdeli-Hahn A et al. Detection of human herpesvirus-6 in mesial temporal lobe epilepsy surgical brain resections. Neurology 2003; 61: 1405-1411*
70. *Theodore WH, Epstein L, Gaillard WD et al. Human herpes virus 6B: a possible role in epilepsy? Epilepsia 2008; 49: 1828-1837*
71. *Bien CG, Urbach H, Schramm J et al. Limbic encephalitis as a precipitating event in adult-onset temporal lobe epilepsy. Neurology 2007; 69: 1236-1244*
72. *Bauer J, Vezzani A, Bien CG. Epileptic encephalitis: the role of the innate and adaptative immune system. Brain Pathol 2012; 22: 412-421*
73. *Moscato EH, Jain A, Peng X. Mechanisms underlying autoimmune synaptic encephalitis leading to disorders of memory, behavior and cognition: insights from molecular, cellular and synaptic studies. Eur J Neurosci 2010; 32: 298-309*
74. *Pleasure D. Diagnostic and pathogenic significance of glutamate receptor autoantibodies. Arch Neurol 2008; 65: 589-592*
75. *Benarroch E. NMDA receptors: recent insights and clinical correlations. Neurology 2011; 76: 1750-1757*
76. *Panzer JA, Gleichman AJ, Lynch DR. Glutamatergic autoencephalitides: an emerging field. J Neural Transm 2014; Jan 9 Epub ahead of print*
77. *Ances B, Vitaliani R, Taylor RA et al. Treatment-responsive limbic encephalitis identified by neuropil antibodies: MRI and PET correlates. Brain 2005; 128: 1764-1777*
78. *Vitaliani R, Mason W, Ances B et al. Paraneoplastic encephalitis, psychiatric symptoms, and hypoventilation in ovarian teratoma. Ann Neurol 2005; 58: 594-604*
79. *Dalmau J, Tüzün E, Wu HY et al. Paraneoplastic anti-N-methyl-D-aspartate receptor encephalitis associated with ovarian teratoma. Ann Neurol 2007; 61: 25-36*
80. *Kamei S. Acute juvenile female non-herpetic encephalitis: AJFNHE [in Japanese]. Adv Neurol Sci 2004; 48: 827-836*
81. *Iizuka T, Sakai F, Ide T et al. Anti-NMDA receptor encephalitis in Japan. Neurology 2008; 70: 504-511*
82. *Dalmau J, Gleichman AJ, Hughes EG et al. Anti-NMDA-receptor encephalitis: case series and analysis of the effects of antibodies. Lancet Neurol 2008; 7: 1091-1098*
83. *Florance NR, Davis RL, Lam C et al. Anti-N-methyl-D-aspartate receptor (NMDAR) encephalitis in children and adolescents. Ann Neurol 2009; 66: 11-18*
84. *Dale RC, Irani SR, Brilot F et al. N-methyl-D-aspartate receptor antibodies in pediatric dyskinetic encephalitis lethargica. Ann Neurol 2009; 66: 704-709*
85. *Kumar MA, Jain A, Dechant VE et al. Anti-N-methyl-D-aspartate receptor encephalitis during pregnancy. Arch Neurol 2010; 67: 884-887*
86. *Titulaer MJ, McCracken L, Gabilondo I et al. Late-onset anti-NMDA receptor encephalitis. Neurology 2013; 81: 1058-1063*
87. *Kayser MS, Titulaer MJ, Gresa-Arribas N, Dalmau J. Frequency and characteristics of isolated psychiatric episodes in anti-N-methyl-D-aspartate receptor encephalitis. JAMA Neurol 2013; 70: 1133-1139*
88. *Reid DK, Clardy SL. Neurological picture. Anti-NMDA-receptor encephalitis: unusual presentation of an uncommon condition. J Neurol Neurosurg Psychiatry 2013; 84: 69-70*
89. *Greiner H, Leach JL, Lee KH, Krueger DA. Anti-NMDA receptor encephalitis presenting with imaging findings and clinical features mimicking Rasmussen syndrome. Seizure 2011; 20: 266-270*
90. *Baizabal-Carvallo JF, Stocco A, Muscal E, Jankovic J. The spectrum of movement disorders in children with anti-NMDA receptor encephalitis. Mov Disord 2013; 28: 543-547*
91. *Outteryck O, Baille G, Hodel J et al. Extensive myelitis associated with anti-NMDA receptor antibodies. BMC Neurol 2013; Dec 27; 13: 211. Doi: 10.1186/1471-2377-12-211*
92. *Ishikawa Y, Ikeda K, Murata K et al. Ophthalmoplegia and flaccid paraplegia in a patient with anti-NMDA receptor encephalitis: a case report and literature review. Intern Med 2013; 52: 2811-2815*
93. *Labate A, Quattrone A, Dalmau J, Gambardella A. Anti-N-methyl-D-aspartate-glutamic receptor encephalitis presenting as paroxysmal exercise-induced foot weakness. Mov Disord 2013; 28: 820-822*
94. *Trojanowski JQ, Hickey WF. Human teratomas express differentiated neural antigens. An immunohistochemical study with anti-neurofilament, anti-glial filament, and anti-myelin basic protein monoclonal antibodies. Am J Pathol 1984; 115: 383-389*
95. *Tachibana N, Shirakawa T, Ishii K et al. Expression of various glutamate receptors including N-methyl-D-aspartate receptor (NMDAR) in an ovarian teratoma removed from a young woman with anti-NMDAR encephalitis. Intern Med 2010; 49: 2167-2173*
96. *Gleichman AJ, Spruce LA, Dalmau J et al. Anti-NMDA receptor encephalitis antibody binding is dependent on amino acid identity of a small region within the GluN1 amino terminal domain. J Neurosci 2012; 32: 11082-11094*
97. *Hughes EG, Peng X, Gleichman AJ et al. Cellular and synaptic mechanisms of anti-NMDA receptor encephalitis. J Neurosci 2010; 30: 5866-5875*
98. *Mikasova L, De Rossi P, Bouchet D et al. Disrupted surface cross-talk between NMDA and Ephrin-B2 receptors in anti-NMDA encephalitis. Brain 2012; 135: 1606-1621*
99. *Manto M, Dalmau J, Didelot A et al. Afferent facilitation of corticomotor responses is increased by IgGs of patients with NMDA-receptor antibodies. J Neurol 2011; 258: 27-33*
100. *Kaplan PW, Sutter R. Electroencephalography of autoimmune limbic encephalopathy. J Clin Neurophysiol 2013; 30: 490-504*
101. *Bayreuther C, Bourg V, Dellamonica J et al. Complex partial status epilepticus revealing anti-NMDA receptor encephalitis. Epileptic Disord 2009; 11: 261-265*
102. *Johnson N, Henry C, Fessler AJ, Dalmau J. Anti-NMDA receptor encephalitis causing prolonged nonconvulsive status epilepticus. Neurology 2010; 75: 1480-1482*
103. *Kirkpatrick MP, Clarke CD, Sonmezturk HH, Abou-Khalil B. Rhythmic delta activity represents a form of nonconvulsive status epilepticus in anti-NMDA receptor antibody encephalitis. Epilepsy Behav 2011; 20: 392-394*
104. *Kaplan PW, Rossetti AO, Kaplan EH, Wieser HG. Proposition: limbic encephalitis may represent limbic status epilepticus. A review of clinical and EEG characteristics. Epilepsy Behav 2012; 24: 1-6*
105. *Schmitt SE, Pargeon K, Frechette ES et al. Extreme delta brush: a unique*

EEG pattern in adults with anti-NMDA receptor encephalitis. Neurology 2012; 79: 1094-1100

106. *Nosadini M, Boniver C, Zuliani L et al. Longitudinal electroencephalographic (EEG) findings in pediatric anti-N-methyl-D-aspartate (anti-NMDA) receptor encephalitis: the Padua experience. J Child Neurol 2014; Jan 5 Epub ahead of print*
107. *Niehusmann P, Dalmau J, Rudlowski C et al. Diagnostic value of N-methyl-D-aspartate receptor antibodies in women with new-onset epilepsy. Arch Neurol 2009; 66: 458-464*
108. *Dalmau J, Lancaster E, Martinez-Hernandez E et al. Clinical experience and laboratory investigations in patients with anti-NMDAR encephalitis. Lancet Neurol 2011; 10: 63-74*
109. *Gresa-Arribas N, Titulaer MJ, Torrents A et al. Antibody titres at diagnosis and during follow-up of anti-NMDA receptor encephalitis: a retrospective study. Lancet Neurol 2014; 13: 167-177*
110. *Malter MP, Elger CE, Surges R. Diagnostic value of CSF findings in antibody-associated limbic and anti-NMDAR-encephalitis. Seizure 2013; 22: 136-140*
111. *Martinez-Hernandez E, Horvath J, Shiloh-Malawsky Y et al. Analysis of complement and plasma cells in the brain of patients with anti-NMDAR encephalitis. Neurology 2011; 77: 589-593*
112. *Hansen HC, Klingbeil C, Dalmau J et al. Persistent intrathecal antibody synthesis 15 years after recovering from anti-N-methyl-D-aspartate receptor encephalitis. JAMA Neurol 2013; 70: 117-119*
113. *Maeder-Ingvar M, Prior JO, Irani SR et al. FDG-PET hyperactivity in basal ganglia correlating with clinical course in anti-NMDA-R antibodies encephalitis. J Neurol Neurosurg Psychiatry 2011; 82: 235-236*
114. *Leypoldt F, Buchert R, Kleiter I et al. Fluorodeoxyglucose positron emission tomography in anti-N-methyl-D-aspartate receptor encephalitis: distinct pattern of disease. J Neurol Neurosurg Psychiatry 2012; 83: 681-686*
115. *Titulaer MJ, McCracken L, Gabilondo I et al. Treatment and prognostic factors for long-term outcome in patients with anti-NMDA receptor encephalitis: an observational study. Lancet Neurol 2013; 12: 157-165*
116. *Gabilondo I, Saiz A, Galan L et al. Analysis of relapses in anti-NMDAR encephalitis. Neurology 2011; 77: 996-999*
117. *Breese EH, Dalmau J, Lennon VA et al. Anti-N-methyl-D-aspartate receptor encephalitis: early treatment is beneficial. Pediatr Neurol 2010; 42: 213-214*
118. *Wong-Kisiel LC, Ji T, Renaud DL et al. Response to immunotherapy in a 20-month-old boy with anti-NMDA receptor encephalitis. Neurology 2010; 74: 1550-1551*
119. *Armangue T, Titulaer MJ, Malaga I et al. Pediatric anti-N-methyl-D-aspartate receptor encephalitis – clinical analysis and novel findings in a series of 20 patients. J Pediatr 2013; 162: 850-856*
120. *Thomas A, Rauschkolb P, Gresa-Arribas N et al. Anti-N-methyl-D-aspartate receptor encephalitis: a patient with refractory illness after 25 months of intensive immunotherapy. JAMA Neurol 2013; Oct 28 Epub ahead of print*
121. *Seki M, Suzuki S, Iizuka T et al. Neurological response to early removal of ovarian teratoma in anti-NMDAR encephalitis. J Neurol Neurosurg Psychiatry 2008; 79: 324-326*
122. *Iizuka T, Yoshii S, Kan S et al. Reversible brain atrophy in anti-NMDA receptor encephalitis: a long-term observational study. J Neurol 2010; 257: 1686-1691*
123. *Evoli A, Spinelli P, Frisullo G et al. Spontaneous recovery from anti-NMDAR encephalitis. J Neurol 2012; 259: 1964-1966*
124. *Gumbinger C, Hametner C, Wildemann B et al. Administration of isoflurane-controlled dyskinetic movements caused by anti-NMDAR encephalitis. Neurology 2013; 80: 1997-1998*
125. *Prüss H, Finke C, Höltje M et al. N-methyl-D-aspartate receptor antibodies in herpes simplex encephalitis. Ann Neurol 2012; 72: 902-911*
126. *Leypoldt F, Titulaer MJ, Aguilar E et al. Herpes simplex virus-1 encephalitis can trigger anti-NMDA receptor encephalitis: case report. Neurology 2013; 81: 1637-1639*
127. *Mackay G, Ahmad K, Stone J et al. NMDA receptor autoantibodies in sporadic Creutzfeldt-Jakob disease. J Neurol 2012; 259: 1979-1981*
128. *Grau-Rivera O, Sanchez-Valle R, Saiz A et al. Determination of neuronal antibodies in suspected and definite Creutzfeldt-Jakob disease. JAMA Neurol 2014; 71: 74-78*
129. *Armangue T, Leypoldt F, Malaga I et al. Herpes simplex virus encephalitis is a trigger of brain autoimmunity. Ann Neurol 2013; Dec 8 Epub ahead of print*
130. *Tojo K, Nitta K, Ishii W et al. A young man with anti-NMDAR encephalitis following Guillain-Barré syndrome. Case Rep Neurol 2013; 3: 7-13*
131. *Prüss H, Höltje M, Maier N et al. IgA NMDA receptor antibodies are markers of synaptic immunity in slow cognitive impairment. Neurology 2012; 78: 1743-1753*
132. *Steiner J, Walter M, Glanz W et al. Increased prevalence of diverse N-methyl-D-aspartate glutamate receptor antibodies in patients with an initial diagnosis of schizophrenia: specific relevance of IgG Nr1a antibodies for distinction from N-methyl-D-aspartate glutamate receptor encephalitis. JAMA Psychiatry 2013; 70: 271-278*
133. *Hammer C, Stepinak B, Schneider A et al. Neuropsychiatric disease relevance of circulating anti-NMDA receptor autoantibodies depends on blood-brain barrier integrity. Mol Psychiatry 2013; Sep 3 Epub ahead of print*
134. *Deakin J, Lennox BR, Zandl MS. Antibodies to the N-methyl-D-aspartate receptor and other synaptic proteins in psychosis. Biol Psychiatry 2014; 75: 284-291*
135. *Couthino E, Harrison P, Vincent A. Do neuronal autoantibodies cause psychosis? A neuroimmunological perspective. Biol Psychiatry 2014; 75: 269-275*
136. *Tan KM, Lennon VA, Klein CJ et al. Clinical spectrum of voltage-gated potassium channel autoimmunity. Neurology 2008; 70: 1883-1890*
137. *Jacob S, Irani SR, Rajabally YA et al. Hypothermia in VGKC antibody-associated limbic encephalitis. J Neurol Neurosurg Psychiatry 2008; 79: 202-204*
138. *Cornelius JR, Pittock SJ, McKeon A et al. Sleep manifestations of voltage-gated potassium channel complex autoimmunity. Arch Neurol 2011; 68: 733-738*
139. *Liguori R, Vincent A, Clover L et al. Morvan's syndrome: peripheral and central nervous and cardiac involvement with antibodies to voltage-gated potassium channels. Brain 2001; 124: 2417-2426*
140. *Barajas RF, Collins DE, Cha S, Geschwind MD. Adult-onset drug-refractory seizure disorder associated with anti-voltage-gated potassium – channel antibody. Epilepsia 2010; 51: 473-477*
141. *Suleiman J, Wright S, Gill D et al. VGKC antibodies in pediatric encephalitis presenting with status epilepticus. Neurology 2011; 76: 1252-1255*
142. *Yoo JY, Hirsch LJ. Limbic encephalitis associated with anti-voltage-gated potassium channel complex antibodies mimicking Creutzfeldt-Jakob disease. JAMA Neurol 2014; 71: 79-82*
143. *Olberg H, Haugen M, Storstein A, Vedeler CA. Neurological manifestations related to level of voltage-gated potassium channel antibodies. J Neurol Neurosurg Psychiatry 2013; 84: 941-943*
144. *Vincent A, Buckley C, Schott JM et al. Potassium channel antibody-asso-*

ciated encephalopathy: a potentially immunotherapy-responsive form of limbic encephalitis. Brain 2004; 127: 701-712

145. *Lai M, Huijbers MG, Lancaster E et al. Investigation of LGI1 as the antigen in limbic encephalitis previously attributed to potassium channels: a case series. Lancet Neurol 2010; 9: 776-785*
146. *Irani SR, Alexander S, Waters P et al. Antibodies to Kv1 potassium channel-complex proteins leucine-rich, glioma inactivated 1 protein and contactin-associated protein-2 in limbic encephalitis, Morvan's syndrome and acquired neuromyotonia. Brain 2010; 133: 2734-2748*
147. *Klein CJ, Lennon VA, Aston PA et al. Insights from LGI1 and CASPR2 potassium channel complex autoantibody subtyping. JAMA Neurol 2013; 70: 229-234*
148. *Wong SH, Saunders MD, Larner AJ et al. An effective immunotherapy regimen for VGKC antibody-positive limbic encephalitis. J Neurol Neurosurg Psychiatry 2010; 81: 1167-1169*
149. *Gast H, Schindler K, Z'graggen WJ, Hess CW. Improvement of non-paraneoplastic voltage-gated potassium channel antibody-associated limbic encephalitis without immunosuppressive therapy. Epilepsy Behav 2010; 17: 555-557*
150. *Kalachikov S, Evgrafov O, Ross B et al. Mutations in LGI1 cause autosomal-dominant partial epilepsy with auditory features. Nat Genet 2002; 30: 335-341*
151. *Cash SS, Larvie M, Dalmau J. Case 34-2011: A 75-year-old man with memory loss and partial seizures. N Engl J Med 2011; 365: 1825-1833*
152. *Chabrol E, Navarro V, Provenzano G et al. Electroclinical characterization of epileptic seizures in leucine-rich, glioma-inactivated 1-deficient mice. Brain 2010; 133: 2749-2762*
153. *Irani SR, Michell AW, Lang B et al. Faciobrachial dystonic seizures precede Lgi1 antibody limbic encephalitis. Ann Neurol 2011; 69: 892-900*
154. *Andrade DM, Tai P, Dalmau J, Wennberg R. Tonic seizures: a diagnostic clue of anti-LGI1 encephalitis. Neurology 2011; 76: 1355-1357*
155. *Irani SR, Stagg CJ, Schott JM et al. Faciobrachial dystonic seizures: the influence of immunotherapy on seizure control and prevention of cognitive impairment in a broadening phenotype. Brain 2013; 136: 3151-3162*
156. *Tofaris GK, Irani SR, Cheeran BJ et al. Immunotherapy-responsive chorea as the presenting feature of LGI1-antibody encephalitis. Neurology 2012; 79: 195-196*
157. *Ohkawa T, Fukata Y, Yamasaki M et al. Autoantibodies to epilepsy-related LGI1 in limbic encephalitis neutralize LGI-ADAM22 interaction and reduce synaptic AMPA receptors. J Neurosci 2013; 33: 18161-18174*
158. *Plantone D, Renna R, Grossi D et al. Teaching Neuroimages: Basal ganglia involvement in facio-brachial dystonic seizures associated with LGI1 antibodies. Neurology 2013; 80: e183-184; Erratum in: Neurology 2013; 80: 2018*
159. *Lancaster E, Huijbers MG, Bar V et al. Investigations of Caspr2, an autoantigen of encephalitis and neuromyotonia. Ann Neurol 2011; 69: 303-311*
160. *Krogias C, Hoepner R, Müller A et al. Successful treatment of anti-Caspr2 syndrome by interleukin 6 receptor blockade through tocilizumab. JAMA Neurol 2013; 70: 1056-1059*
161. *Patel AB, de Graaf RA, Martin DL et al. Evidence that GAD65 mediates increased GABA synthesis during intense neuronal activity in vivo. J Neurochem 2006; 97: 385-396*
162. *Stagg CJ, Lang B, Best JG et al. Autoantibodies to glutamic acid decarboxylase in patients with epilepsy are associated with low cortical GABA levels. Epilepsia 2010; 51: 1898-1901*
163. *Mitoma H, Ishida K, Shizuka-Ikeda M, Mizusawa H. Dual impairment of GABAA- and GABAB-receptor-mediated synaptic responses by autoantibodies to glutamic acid decarboxylase. J Neurol Sci 2003; 208: 51-56*
164. *Hosoi Y, Suzuki-Sakao M, Terada T et al. GABA-A receptor impairment in cerebellar ataxia with anti-glutamic acid decarboxylase antibodies. J Neurol 2013; 260: 3086-3092*
165. *Burton AR, Baquet Z, Eisenbarth GS et al. Central nervous system destruction mediated by glutamic acid decarboxylase-specific CD4+ T cells. J Immunol 2010; 184: 4863-4870*
166. *Manto MU, Laute MA, Aquera M et al. Effects of anti-glutamic acid decarboxylase antibodies associated with neurological diseases. Ann Neurol 2007; 61: 544-551*
167. *Vianello M, Keir G, Giometto B et al. Antigenic differences between neurological and diabetic patients with anti-glutamic acid decarboxylase antibodies. Eur J Neurol 2005; 12: 294-299*
168. *Saiz A, Blanco Y, Sabater L et al. Spectrum of neurological syndromes associated with glutamic acid decarboxylase antibodies: diagnostic clues for this association. Brain 2008; 131: 2553-2563*
169. *Akbarian S, Huang S. Molecular and cellular mechanisms of altered GAD1/GAD67 expression in schizophrenia and related disorders. Brain Res Rev 2006; 52: 293-304*
170. *Thompson M, Weickert CS, Wyatt E, Webster MJ. Decreased glutamic acid decarboxylase(67) mRNA expression in multiple brain areas of patients with schizophrenia and mood disorders. J Psychiatry Res 2009; 43: 970-977*
171. *Kalkman HO, Loetscher E. GAD(67): the link between the GABA-deficit hypothesis and the dopaminergic- and glutaminergic theories of psychosis. J Neural Transm 2003; 110: 803-812*
172. *Najjar D, Pearlman D, Zagzag D et al. Glutamic acid decarboxylase autoantibody syndrome presenting as schizophrenia. Neurologist 2012; 18: 86-91*
173. *Honnorat J, Saiz A, Giometto B et al. Cerebellar ataxia with anti-glutamic acid decarboxylase antibodies: study of 14 patients. Arch Neurol 2001; 58: 225-230*
174. *Yoshimoto T, Doi M, Fukai N et al. Type 1 diabetes mellitus and drug-resistant epilepsy: presence of high titer of anti-glutamic acid decarboxylase autoantibodies in serum and cerebrospinal fluid. Intern Med 2005; 44: 1174-1177*
175. *Vulliemoz S, Vanini G, Truffert A et al. Epilepsy and cerebellar ataxia associated with anti-glutamic acid decarboxylase antibodies. J Neurol Neurosurg Psychiatry 2007; 78: 187-189*
176. *Errichiello L, Perruolo G, Pascarella A et al. Autoantibodies to glutamic acid decarboxylase (GAD) in focal and generalized epilepsy: a study on 233 patients. J Neuroimmunol 2009; 211: 120-123*
177. *Falip M, Careno M, Miro J et al. Prevalence and immunological spectrum of temporal lobe epilepsy with glutamic acid decarboxylase antibodies. Eur J Neurol 2012; 19: 827-833*
178. *Chang T, Alexopoulos H, McMenamin M et al. Neuronal surface and glutamic acid decarboxylase autoantibodies in nonparaneoplastic stiff person syndrome. JAMA Neurol 2013; 70: 1140-1149*
179. *Veri K, Uibo O, Talvik T et al. Newly-diagnosed pediatric epilepsy is associated with elevated autoantibodies to glutamic acid decarboxylase but not cardiolipin. Epilepsy Res 2013; 105: 86-91*
180. *Kanter IC, Huttner HB, Staykov D et al. Cyclophosphamide for anti-GAD antibody-positive refractory status epilepticus. Epilepsia 2008; 49: 914-920*
181. *Cikrikcili U, Ulusoy C, Turan S et al. Non-convulsive status epilepticus associated with glutamic acid decarboxylase antibody. Clin EEG Neurosci*

2013; 44: 232-236
182. Giometto B, Nicolao P, Macucci M et al. Temporal-lobe epilepsy associated with glutamic-acid decarboxylase autoantibodies. Lancet 1998; 352: 457
183. Marchiori GC, Vaglia A, Vianello M et al. Encephalitis associated with glutamic acid decarboxylase autoantibodies. Neurology 2001; 56: 814
184. Mata S, Muscas GC, Naldi I et al. Non-paraneoplastic limbic encephalitis associated with anti-glutamic acid decarboxylase antibodies. J Neuroimmunol 2008; 199: 155-159
185. Blanc F, Ruppert E, Kleitz C et al. Acute limbic encephalitis and glutamic acid decarboxylase antibodies: a reality? J Neurol Sci 2009; 287: 69-71
186. Malter MP, Helmstaedter C, Urbach H et al. Antibodies to glutamic acid decarboxylase define a form of limbic encephalitis. Ann Neurol 2010; 67: 470-478
187. Korff C, Parvex P, Cimasoni L et al. Encephalitis associated with glutamic acid decarboxylase autoantibodies in a child: a treatable condition? Arch Neurol 2011; 68: 1065-1068
188. Mirabelli-Badenier M, Morana G, Pinto F et al. Anti-glutamic acid decarboxylase limbic encephalitis without epilepsy evolving into dementia with cerebellar ataxia. Arch Neurol 2012; 69: 1064-1066
189. Lai M, Hughes EG, Peng X et al. AMPA receptor antibodies in limbic encephalitis alter synaptic receptor location. Ann Neurol 2009; 65: 424-434
190. Bataller L, Galiano R, Garcia-Escriq M et al. Reversible paraneoplastic limbic encephalitis associated with antibodies to the AMPA receptor. Neurology 2010; 74: 265-267
191. Wei YC, Liu CH, Lin JJ et al. Rapid progression and brain atrophy in anti-AMPA receptor encephalitis. J Neuroimmunol 2013; 261: 129-133
192. Lancaster E, Lai M, Peng X et al. Antibodies to the GABA(B) receptor in limbic encephalitis with seizures: case series and characterisation of the antigen. Lancet Neurol 2010; 9: 67-76
193. Boronat A, Sabater L, Saiz A et al. GABA(B) receptor antibodies in limbic encephalitis and anti-GAD-associated neurologic disorders. Neurology 2011; 76: 795-800
194. Jarius S, Steinmeyer F, Knobel A et al. GABAB receptor antibodies in paraneoplastic cerebellar ataxia. J Neuroimmunol 2013; 256: 94-96
195. Mundiyanapurath S, Jarius S, Probst C et al. GABA-B-receptor antibodies in paraneoplastic brainstem encephalitis. J Neuroimmunol 2013; 259: 88-91
196. Höftberger R, Titulaer MJ, Sabater L et al. Encephalitis and GABAB receptor antibodies: novel findings in a new case series of 20 patients. Neurology 2013; 81: 1500-1506
197. Jeffery OJ, Lennon VA, Pittock SJ et al. GABAB receptor autoantibody frequency in service serologic evaluation. Neurology 2013; 81: 882-887
198. Ohta K, Seki M, Dalmau J, Shinohara Y. Perfusion IMP-SPECT shows reversible abnormalities in GABA(B) receptor antibody associated encephalitis with normal MRI. Brain Behav 2011; 1: 70-72
199. Boronat A, Gelfand JM, Gresa-Arribas N et al. Encephalitis and antibodies to dipeptidyl-peptidase-like protein-6, a subunit of Kv4.2 potassium channels. Ann Neurol 2013; 73: 120-128
200. Armangue T, Titulaer MJ, Sabater L et al. A novel treatment-responsive encephalitis with frequent opsoclonus and teratoma. Ann Neurol 2013; Apr 24 Epub ahead of print
201. Whiteley AM, Swash M, Urich H. Progressive encephalomyelitis with rigidity. Brain 1976; 99: 27-42
202. Casado JL, Gil-Peralta A, Graus F et al. Anti-Ri antibodies associated with opsoclonus and progressive encephalomyelitis with rigidity. Neurology 1994; 44: 1521-1522
203. Shugaiv E, Leite MI, Sehitoglu E et al. Progressive encephalomyelitis with rigidity and myoclonus: a syndrome with diverse clinical features and antibody responses. Eur Neurol 2013; 69: 257-262
204. Mas N, Saiz A, Leite MI et al. Antiglycine-receptor encephalomyelitis with rigidity. J Neurol Neurosurg Psychiatry 2011; 82: 1399-1401
205. Iizuka T, Leite MI, Lang B et al. Glycine receptor antibodies are detected in progressive encephalomyelitis with rigidity and myoclonus (PERM) but not in saccadic oscillations. J Neurol 2012; 259: 1566-1573
206. Peeters E, Vanacker P, Woodhall M et al. Supranuclear gaze palsy in glycine receptor antibody-positive progressive encephalomyelitis with rigidity and myoclonus. Mov Disord 2012; 27: 1830-1832
207. McKeon A, Martinez-Hernandez E, Lancaster E et al. Glycine receptor autoimmune spectrum with stiff-man syndrome phenotype. JAMA Neurol 2013; 70: 44-50
208. Carr I. The Ophelia syndrome: memory loss in Hodgkin's disease. Lancet 1982; 319: 844-845
209. Lancaster E, Martinez-Hernandez E, Titulaer MJ et al. Antibodies to metabotropic glutamate receptor 5 in Ophelia syndrome. Neurology 2011; 77: 1698-1701
210. Mat A, Adler H, Merwick A et al. Ophelia syndrome with metabotropic glutamate receptor 5 antibodies in CSF. Neurology 2013; 80: 1349-1350
211. Jabbari B, Huott AD. Seizures in thyrotoxicosis. Epilepsia 1980; 21: 91-96
212. Su YH, Izumi T, Kitsu M, Fukuyama Y. Seizure threshold in juvenile myoclonic epilepsy with Graves disease. Epilepsia 1993; 34: 488-492
213. Aydin A, Cemeroglu AP, Baklan B. Thyroxine-induced hypermotor seizure. Seizure 2004; 13: 61-65
214. Brain L, Jellinek EH, Ball K. Hashimoto's disease and encephalopathy. Lancet 1966; 288: 512-514
215. Kothbauer-Margreiter I, Sturzenegger M, Komor J et al. Encephalopathy associated with Hashimoto thyroiditis: diagnosis and treatment. J Neurol 1996; 243: 585-593
216. Chong JY, Rowland LP, Utiger RD. Hashimoto encephalopathy: syndrome or myth? Arch Neurol 2003; 60: 164-171
217. Chaudhuri A, Behan PO. The clinical spectrum, diagnosis, pathogenesis and treatment of Hashimoto's encephalopathy (recurrent acute disseminated encephalomyelitis). Curr Med Chem 2003; 10: 1945-1953
218. Castillo P, Woodruff B, Caselli R et al. Steroid-responsive encephalopathy associated with autoimmune thyroiditis. Arch Neurol 2006; 63: 197-202
219. Mocellin R, Walterfang M, Velakoulis D. Hashimoto's encephalopathy: epidemiology, pathogenesis and management. CNS Drugs 2007; 21: 799-811
220. Schiess N, Pardo CA. Hashimoto's encephalopathy. Ann N Y Acad Sci 2008; 1142: 254-265
221. Rüegg S. [Thyroid and epilepsy]. Epileptologie 2011; 28: 30-41 (German)
222. Schäuble B, Castillo PR, Boeve BF, Westmoreland BF. EEG findings in steroid-responsive encephalopathy associated with autoimmune thyroiditis. Clin Neurophysiol 2003; 114: 32-37
223. Hartmann M, Schaner B, Scheglmann K et al. [Hashimoto encephalopathy: steroid-sensitive encephalopathy in Hashimoto thyroiditis]. Nervenarzt 2000; 71: 489-494 (German)
224. Williams GR. Neurodevelopmental and neurophysiological actions of thyroid hormone. J Neuroendocrinol 2008; 20: 784-794
225. Whiting S, Camfield P, Arab D, Salisbury S. Insulin-dependent diabetes mellitus presenting in children as frequent, medically unresponsive, partial seizures. J Child Neurol 1997; 12: 178-180

226. *Olson JA, Olson DM, Sandborg C et al. Type 1 diabetes mellitus and Epilepsia partialis continua in a 6-year-old boy with elevated anti-GAD65 antibodies. Pediatrics 2002; 109: E50*
227. *McCorry D, Nicolson A, Smith D et al. An association between type 1 diabetes and idiopathic generalized epilepsy. Ann Neurol 2006; 59: 204-206*
228. *Mancardi MM, Striano P, Giannattasio A et al. Type 1 diabetes and epilepsy: more than a casual association. Epilepsia 2010; 51: 320-321*
229. *Ramakrishnan R, Appleton R. Study of the prevalence of epilepsy in children with type 1 diabetes mellitus. Seizure 2012; 21: 292-294*
230. *O'Connell MA, Harvey AS, Mackay MT, Cameron FJ. Does epilepsy occur more frequently in children with type 1 diabetes? J Paediatr Child Health 2008; 44: 586-589*
231. *Verrotti A, Scaparrotta A, Olivieri C, Chiarelli F. Seizures and type 1 diabetes mellitus: current state of knowledge. Eur J Endocrinol 2012; 167: 749-758*
232. *Shi Y, Kanaani J, Menard-Rose V et al. Increased expression of GAD65 and GABA in pancreatic ß-cells impairs first-phase insulin secretion. Am J Physiol Endocrinol Metab 2000; 279: E684-E694*
233. *Vulliemoz S, Seeck M. An association between type 1 diabetes and idiopathic generalized epilepsy. Ann Neurol 2006; 59: 728*
234. *Rüegg S. Anti-glutamic acid decarboxylase antibodies – the missing link between epilepsy and diabetes. Ann Neurol 2006; 59: 728-729*
235. *Dressler A, Reithofer E, Trimmel-Schwahofer P et al. Type 1 diabetes and epilepsy: efficacy and safety of the ketogenic diet. Epilepsia 2010; 51: 1086-1089*
236. *Schober E, Otto KP, Dost A et al. Association of epilepsy and type 1 diabetes mellitus in children and adolescents: is there an increased risk for diabetic ketoacidosis? J Pediatr 2012; 160: 662-666*
237. *Pavone P, Striano P, Falsaperla R et al. Infantile spasms syndrome, West syndrome and related phenotypes: What we know in 2013. Brain Dev 2013; Nov 19 Epub ahead of print*
238. *Quek AM, Britton JW, McKeon A et al. Autoimmune epilepsy: clinical characteristics and response to immunotherapy. Arch Neurol 2012; 69: 582-593*
239. *Rüegg S, Panzer JA. Immune therapy for pharmacoresistant epilepsy – reday to go? Neurology 2014 (in press)*

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