Epileptologie | 31. Jahrgang April | 2014 ISSN 1660-3656

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Inhalt

Schweizerische Liga gegen Epilepsie
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Lega Svizzera contro l'Epilessia
Swiss League Against Epilepsy

Richtlinien für die Autoren

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Was ist an die Redaktion einzureichen?

Alle Manuskripte sind inklusive Abbildungen und Tabellen in dreifacher Ausführung einzureichen. Bevorzugt wird eine elektronische Manuskripteinreichung per e-mail (Textverarbeitung: MS Word), alternativ die Zusendung von drei Ausdrucken und einer CD (für Abb. und Tab. ist das verwendete Programm anzugeben).

Epilepsie und Autoimmunität

Dr. med. Christian Korff

Die Rolle der Autoimmunität bei Epilepsien wird seit vielen Jahren untersucht. Fortschritte auf diesem Gebiet sind insofern zu verzeichnen, als kein Zweifel mehr besteht, dass bei gewissen Epilepsieformen eine entzündliche Reaktion im Vordergrund steht, sei das beim Anfallsursprung oder bei den Langzeitfolgen der Erkrankung. Im Zusammenhang mit dieser faszinierenden Erkenntnis diskutiert die International League against Epilepsy (ILAE) im Moment darüber, die Kategorie „immun" in ihr Organisationsschema der Epilepsien aufzunehmen.

Die verschiedenen in dieser Ausgabe der Zeitschrift präsentierten Artikel bieten eine Übersicht über den Wissensstand auf diesem Gebiet und sollen damit den Leserinnen und Lesern das interessante Forschungsfeld näher bringen.

Stephan Rüegg und Christian Korff fassen die weltweite Situation diesbezüglich bei Erwachsenen und Kindern zusammen.

Aurélien Viaccoz und Patrice Lalive zeigen verschiedene immun-therapeutische Ansätze, welche in Betracht gezogen werden können, mit der interessanten Perspektive, direkt auf die Ursache der Epilepsie einwirken zu können.

Maria Isabel Vargas Gomez beschreibt die technischen Fortschritte der letzten Jahre in der Bildgebung bei entzündlichen Prozessen des Gehirns.

Schliesslich präsentieren Franz Josef Holzer und Margitta Seeck die Rolle der Autoimmunität beim Status epilepticus.

Wir bedanken uns herzlich bei allen Autoren, die zu dieser Ausgabe der Zeitschrift „Epileptologie" beigetragen haben, und wünschen Ihnen eine angenehme Lektüre.

Christian Korff

Dr. med. Christian Korff

Le rôle de l'autoimmunité dans les épilepsies est étudié depuis de nombreuses années. Les avancées dans le domaine ont été telles qu'il ne fait plus aucun doute que la réponse inflammatoire est impliquée de façon prépondérante dans certaines formes d'épilepsie, que ce soit dans la génèse des crises ou dans leurs conséquences à long terme. Témoignant de ces progrès passionnants, la Ligue Internationale contre l'Epilepsie discute actuellement d'intégrer une catégorie « immune » dans son schéma d'organisation des épilepsies.

Les différents articles proposés dans ce numéro d'Epileptologie offrent un pointage actualisé des connaissances dans le domaine, qui devrait permettre à tous les lecteurs d'appréhender le sujet de façon éclairée.

Stephan Rüegg et Christian Korff présentent un tableau global résumant la situation chez l'adulte et chez l'enfant, respectivement.

Aurélien Viaccoz et Patrice Lalive se penchent sur les approches thérapeutiques immunes, avec la perspective intéressante, une fois n'est pas coutume, de pouvoir agir directement sur la cause de l'épilepsie chez certains patients.

Maria Isabel Vargas Gomez, présente l'aide que peuvent apporter les techniques d'imagerie cérébrale développées au cours de ces dernières années.

Enfin, Franz Josef Holzer et Margitta Seeck, abordent le rôle de l'autoimmunité dans l'état de mal épileptique.

Nous tenons à remercier chaleureusement tous les auteurs ayant contribué à ce numéro, et vous souhaitons une très bonne lecture!

Christian Korff

Dr. med. Christian Korff

The role of the autoimmunity in the epilepsies has been studied for many years. Advances in the field were such as there is no more doubt that the inflammatory response is implied in certain forms of epilepsies, whether it be in the genesis of seizures or in their consequences on the long term. Given this fascinating progress, the International League against Epilepsy is currently discussing the integration of an "immune" category in its organization scheme of the epilepsies.

The various articles presented in the current issue of Epileptologie offer an updated state of knowledge in the field, which should help readers to apprehend the subject in an enlightened way.

Stephan Rüegg and Christian Korff present a summary of the global situation in adults and in children, respectively.

Aurélien Viaccoz and Patrice Lalive present various therapeutic immune approaches to be considered, with the interesting perspective of being able to act directly on the cause of the epilepsy.

Maria Isabel Vargas Gomez presents the technical advances in imaging of cerebral inflammatory processes developed during these last years.

Lastly, Franz Josef Holzer and Margitta Seeck, present the role of the autoimmunity in status epilepticus.

We would like to wholeheartedly thank all authors who have contributed to this issue, and wish you a pleasant reading!

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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.

Epileptologie 2014; 31: 4 – 25

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) for 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-lymphocytes) 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)

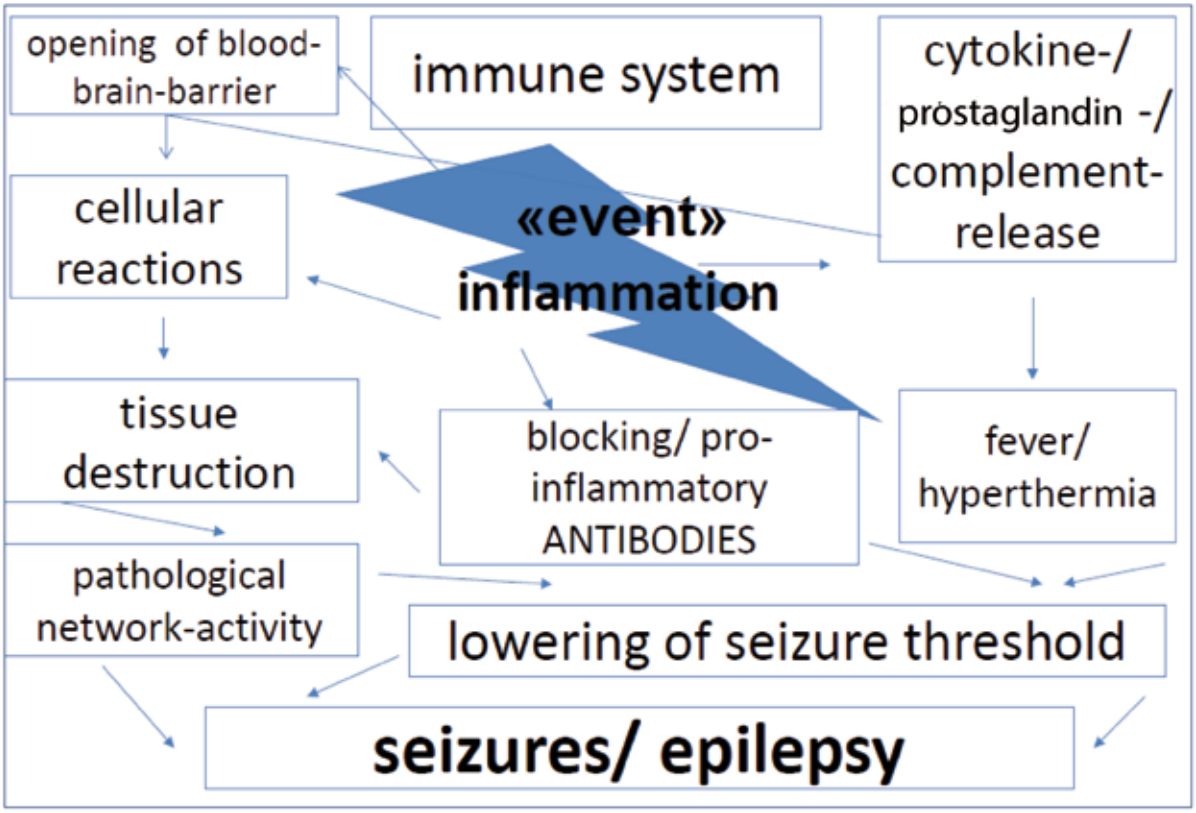

Figure 1: The complex interplay between the immune system and epilepsy

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 immune system
  - 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 course of 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 receptor; GAD: glutamate decarboxylase; LGI1: leucin-rich glioma-inactivated protein-1; mGluR5: metabotropic glutamate receptor-5; NMDAR: N-methyl-D-aspartate receptor; PERM: progressive encephalomyelitis with rigidity and myoclonus; PNP: peripheral neuropathy; RF: rheuma factor; SPS: stiff-person syndrome; SREAT: steroid-responsive encephalopathy associated with autoimmune thyroiditis; SS: Sjögren's syndrome; TPO: thyroid peroxidase; VGCC: voltage-gated calcium channel; VGKC: voltage-gated potassium channel

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

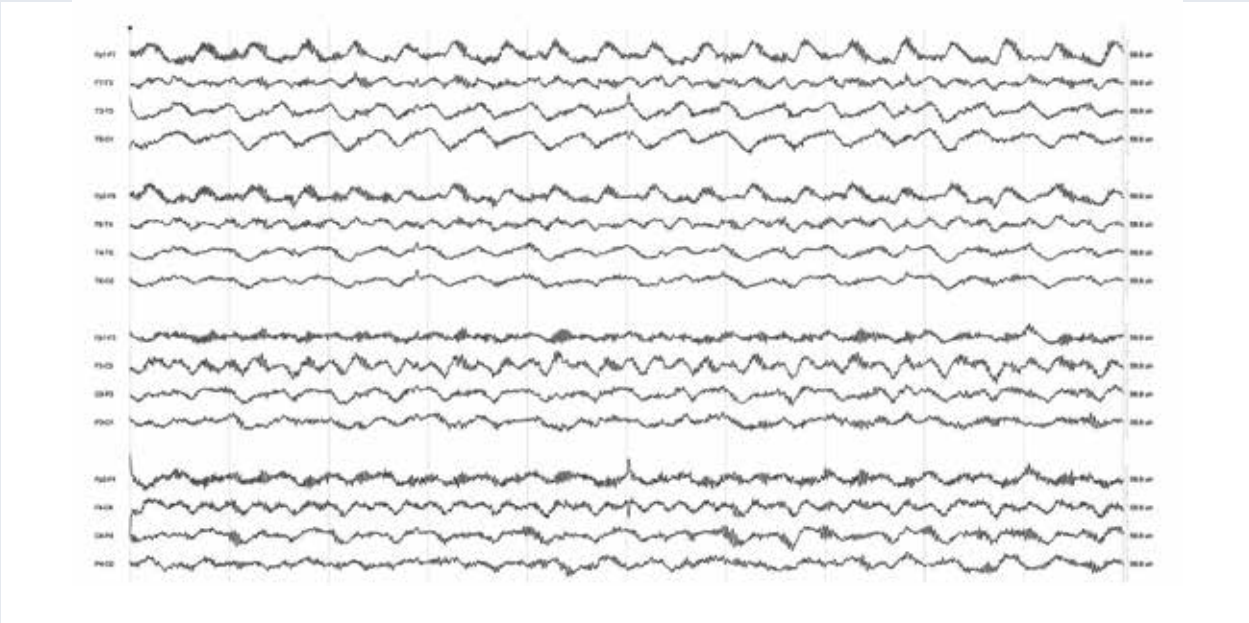

Figure 2: Continuous EEG-recording in a 19-year-old man with anti-NMDA receptor encephalitis associated with dyskinesias, seizures and coma (reprinted from Schmitt et al. [105], with permission from Neurology®)

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 and 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 with 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 suspected 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 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 controls, 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].

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Autoimmunité, épilepsies et encéphalopathies chez l'enfant

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Résumé

L'importance de la réponse immune dans la physiopathologie des crises et des épilepsies est de mieux en mieux connue. De très nombreuses questions sur le sujet restent toutefois ouvertes, tant en ce qui concerne les mécanismes que le diagnostic ou la prise en charge de ce type d'atteinte, et ce, particulièrement chez l'enfant. Le but de cette revue est de donner un aperçu de l'état actuel des connaissances sur les syndromes épileptiques spécifiques et les encéphalopathies de l'enfant dans lesquels un rôle du système immunitaire a été suspecté et étudié.

Epileptologie 2014; 31: 26 – 31

Mots clés : Epilepsie, autoimmunité, enfants

Autoimmunity, Epilepsies and Encephalopathies in Children

The importance of the immune response in the pathophysiology of the epilepsies is better and better known. Many questions remain open, though, and concern underlying mechanisms, diagnostic work-up and treatment options. This is particularily true for children. The aim of this review is to present an update of the current knowledge on the specific pediatric epilepsy syndromes and encephalopathies in which a role of the immune system has been suspected and studied.

Key words: Epilepsy, autoimmunity, children

Autoimmunität, Epilepsie und Enzephalopathie bei Kindern

Die Bedeutung der Immunreaktion in der Pathophysiologie von Epilepsien ist mehr und mehr bekannt. Allerdings bleiben viele Fragen offen. Sie betreffen die zugrunde liegenden Mechanismen, diagnostische Massnahmen und therapeutische Möglichkeiten. Dies trifft besonders bei Kindern zu. Ziel dieses Überblicks ist es, eine Zusammenfassung über den aktuellen Wissensstand bezüglich die speziellen pädiatrischen Epilepsie-Syndrome und Enzephalopathien, bei denen eine Rolle des Immunsystems vermutet und studiert wurde, zu präsentieren.

Schlüsselwörter: Epilepsie, Autoimmunität, Kinder

Introduction

L'importance de la réponse immune dans la physiopathologie des crises et des épilepsies est de plus en plus étudiée, comme en témoigne le nombre sans cesse croissant de publications scientifiques parues dans le domaine au cours de ces dernières années. L'objet de ces travaux de recherche se base aussi bien sur les différentes thérapies immunes utilisées de longue date dans les épilepsies réfractaires, que sur le lien associant la présence de certains autoanticorps à la survenue de crises. Récemment, une équipe a montré que des autoanticorps plasmatiques étaient présents chez 11 (9,7%) des 114 enfants dont les échantillons sanguins étaient analysés dans un intervalle de 6 mois après une première crise épileptique [1]. Dans cette série, les cibles de ces anticorps incluaient certains sous-éléments du complexe du canal potassique voltage-dépendant (VGKC), et le récepteur glutamatergique NMDA. De façon intéressante, la symptomatologie de l'encéphalite qui accompagne classiquement les crises dans ce type de situation chez l'adulte, n'était pas présente de façon constante chez ces enfants.

De très nombreuses questions restent ouvertes, tant en ce qui concerne la physiopathologie que le diagnostic ou la prise en charge de ce type d'atteinte. Ceci est particulièrement le cas chez l'enfant, qui reste paradoxalement le parent pauvre de la recherche dans un domaine qui le concerne pourtant en priorité, la première décennie étant l'une des deux périodes de la vie au cours de laquelle le risque de débuter une épilepsie est le plus élevé. Le but de cette revue est de donner un aperçu de l'état actuel des connaissances sur les syndromes épileptiques spécifiques et les encéphalopathies de l'enfant dans lesquels un rôle du système immunitaire a été suspecté et étudié.

1. Epilepsies et syndromes épileptiques

Convulsions infantiles bénignes

Yoshimura et al. ont rapporté en 2001 la présence, dans le sérum, d'immunoglobulines G (IgG) anticardiolipines (aCL) chez 8/9 (88,9%) patients présentant des convulsions infantiles bénignes [2]. Tous ces enfants, auparavant en bonne santé, présentaient des crises récurrentes en salves, débutant entre 3,5 et 14 mois, et répondant au traitement de carbamazépine administré. Leur EEG était normal, tout comme leur examen neurologique et développemental. Dans cette étude, seul un enfant contrôle (sans aucune pathologie neurologique connue) sur les 6 testés (16,7%) montrait également un taux d'aCL positif, la différence entre les 2 groupes étant significative ($p < 0,01$). Les auteurs précisent que deux de ces patients montraient des résultats d'aCL positifs avant instauration du traitement médicamenteux, réfutant par là l'hypothèse parfois soulevée d'une réponse immune anormale induite par certaines molécules antiépileptiques. Le rôle exact de l'anticorps et le lien de cause à effet avec la présence de crises n'est toutefois pas éclairci, et nous n'avons pas connaissance d'avancées plus récentes confirmant l'hypothèse d'une étiologie immune dans cette entité. Par ailleurs, les développements récents des technologies diagnostiques génétiques ont permis la découverte de mutations sur le gène (*PRRT2*) codant pour une protéine transmembranaire riche en proline, chez plus de 80% des patients atteints de ce même type d'épilepsie [3], reléguant par là toute autre hypothèse étiologique à un plan inférieur.

Syndrome de West

Le syndrome de West est caractérisé par une triade clinique associant des spasmes épileptiques, un EEG montrant une hypsarythmie, et un retard développemental. Dans une proportion importante de cas, la cause de ce syndrome reste inconnue, malgré des investigations extensives. Les corticostéroïdes et, dans une moindre mesure, les immunoglobulines intraveineuses, faisant partie depuis longtemps de l'arsenal thérapeutique efficace dans le traitement du syndrome de West [4, 5], l'hypothèse d'une étiologie immune sous-jacente a été avancée. Les résultats des études en recherche fondamentale ne sont pas légion. Montelli et al., par exemple, rapportent une dysfonction immunitaire globale, incluant une réponse cellulaire anormale et la présence de niveaux anormalement élevés d'immunoglobulines de type G et M, chez des patients atteints d'un syndrome de West [6]. D'un autre côté, le dosage de l'interleukine 6 (IL-6) dans le LCR s'est avéré dans la norme chez les 12 patients avec syndrome de West rapportés par Tekgul et al. [7].

Peu de données récentes étayent ces constatations. Dans un article clinique, Suleiman et al. rapportent la présence, à 13 mois, d'anticorps sériques dirigés contre le complexe VGKC chez un patient présentant, dès l'âge de 4 mois, des spasmes épileptiques en salves, un retard du développement et un EEG correspondant à une hypsarythmie modifiée [8]. On relevait également la présence, dans le LCR, d'une valeur de néoptérine légèrement supérieure à la norme, et des bandes oligoclonales (également présentes dans le sérum, toutefois, et pouvant être dues à un passage à travers la barrière hémato-encéphalique suite à une synthèse extrathécale). L'IRM ne montrait aucun signe inflammatoire, et les autres autoanticorps testés étaient négatifs. Son état clinique et son EEG se sont améliorés de façon significative suite à l'administration de prednisone orale. A notre connaissance, ce cas reste à ce jour isolé. L'étude à plus large échelle de Suleiman citée en introduction, notamment, ne fait pas mention spécifique d'enfants atteints de ce syndrome parmi ceux dont les résultats d'autoanticorps étaient positifs [1].

Syndrome de Landau-Kleffner

Le syndrome de Landau-Kleffner (LKS), ou aphasie épileptique acquise, se manifeste par une aphasie progressive liée à la présence de pointes-ondes continues pendant le sommeil (POCS). L'étiologie de cette entité décrite il y a plus de 50 ans reste inconnue, mais comme pour d'autres entités, la bonne réponse à différentes approches immunomodulatrices observée chez un nombre important de patients laisse suspecter une possible étiologie dysimmune. Connolly et al. ont rapporté une fréquence élevée d'anticorps sériques anti-endothélium chez des patients en étant atteints, dans leur série les comparant à d'autres enfants atteints d'autisme ou d'autres pathologies du système nerveux [9, 10]. Le nombre de patients inclus dans cette étude était toutefois trop petit pour en tirer des conclusions significatives. De façon similaire, des anticorps dirigés contre diverses régions du système nerveux central ont été retrouvés chez les 4 patients atteints d'un LKS rapportés par Boscolo et al., mais la question de savoir si leur présence représente une cause ou une conséquence de l'activité épileptique reste ouverte. Les rares observations histologiques rapportées à ce jour ne permettent pas de confirmer l'hypothèse étiologique autoimmune de ce syndrome [11], et les données récentes tendent à favoriser une étiologie génétique, pour certains de ces patients en tous les cas [12, 13].

2. Encéphalites et encéphalopathies

Encéphalite à anticorps anti-récepteurs NMDA

L'encéphalite liée à la présence d'anticorps dirigés contre les récepteurs glutamatergiques NMDA (NMDA-R), initialement décrite chez l'adulte [14, 15], est également bien connue en pédiatrie [16 - 21]. Dans la plupart des cas, les enfants concernés présentent des crises épileptiques au début de leur symptomatologie [21]. La sémiologie ictale n'est pas spécifique, mais l'EEG peut montrer un pattern évocateur, surtout décrit chez l'adulte, sous la forme d'une activité associant ondes lente de haute amplitude et rythmes bas-voltés de haute fréquence (« extreme Delta-brush ») [21, 22]. Dans la plupart des cas, l'EEG montre une surcharge lente évoquant une encéphalopathie diffuse non-spécifique.

Les crises restent plutôt rares et transitoires, et accompagnent des troubles psychiatriques et comportementaux. La symptomatologie progresse rapidement, et inclut des mouvements anormaux (dyskinésies orofaciales, chorée, dystonie), des troubles cognitifs divers, une dysautonomie, des difficultés respiratoires et des troubles du sommeil. Lorsqu'il est complet, le tableau clinique est si suggestif que certains l'apparentent à un véritable syndrome. Les symptômes, souvent extrêmement sévères, peuvent durer des mois, et engendrent une inquiétude importante chez les familles et les soignants, tant ils sont impressionnants. Même si le pronostic vital peut-être engagé, l'évolution à long terme reste plutôt favorable chez l'enfant, une disparition des symptômes sans aucune séquelle étant de règle [16, 17, 20]. Ceci est probablement d'autant plus le cas que le diagnostic est posé rapidement et qu'une approche immunothérapeutique agressive, pouvant inclure stéroïdes, immunoglobulines intraveineuses, plasmaphérèses, cyclophosphamide et rituximab [20, 21 ,23, 24], est mise en route. Les tumeurs ovariennes décrites en association chez la jeune femme, bien qu'exceptionnelles chez l'enfant, doivent être recherchées et traitées chirurgicalement, le cas échéant.

Crises dystoniques facio-brachiales

Le tableau clinique lié à la présence d'anticorps (Ac) dirigés contre la protéine LGI1 (pour « leucin-rich, glioma inactivated 1 protein ») du VGKC, inclut fréquemment des crises dystoniques touchant typiquement une hémiface et le membre supérieur ipsilatéral. Celles-ci peuvent précéder l'apparition de troubles cognitifs signant l'évolution vers une encéphalite limbique, ou rester isolées. Ce type de crise semble être si spécifique à cette dysfonction immune sous-jacente, que certains considèrent l'association comme un véritable syndrome épileptique [25]. Plusieurs auteurs ont rétrospectivement souligné l'excellente réponse de ce type de crises aux thérapies immunomodulatrices [26]. Une étude prospective récente permet de confirmer ces observations chez l'adulte. Irani et al. rapportent en effet une diminution rapide de > 20% de la fréquence des crises chez 9/10 de leurs patients, avec disparition complète des épisodes au cours des 2 mois qui ont suivi l'addition de corticostéroïdes au traitement antiépileptique instauré initialement [25]. Des observations de crises dystoniques facio-brachiales n'ont, à notre connaissance, pas été rapportées chez l'enfant à ce jour. Dans une des rares séries relatant les résultats d'une analyse d'anticorps dirigés contre le complexe VGKC chez l'enfant, 4/10 (40%) des enfants atteints d'une encéphalopathie aiguë, associant des crises en salves à des troubles cognitifs ou comportementaux, montraient des taux d'Ac anti-VGKC positifs. La symptomatologie ictale chez ces enfants n'y est décrite que partiellement, sous la forme de crises « généralisées » ou « secondairement généralisées » [8].

Encéphalite et anticorps anti-GAD

Des anticorps dirigés contre la décarboxylase de l'acide glutamique (GAD), une enzyme impliquée dans la synthèse de l'acide gamma-aminobutyrique (GABA), ont été retrouvés dans le sérum ou le liquide céphalo-rachidien (LCR) chez certains patients présentant des signes d'encéphalite, comprenant, entre autres, une épilepsie sévère, sans autre facteur étiologique clairement identifié [27, 28]. Certains de ces patients présentent également un diabète de type 1, ou d'autres symptômes neurologiques, comme une ataxie cérébelleuse [27, 29]. De tels anticorps ont par ailleurs été impliqués depuis longtemps dans le syndrome de l'homme rigide (stiff-person syndrome). Certains auteurs ont montré par des techniques d'analyse spectroscopique que la concentration du GABA dans le cortex de patients présentant ce tableau clinique était basse [30]; d'autre part, l'injection de sérum ou de LCR de patients atteints chez des animaux sains permet la reproduction de symptômes similaires [28]. L'activité de l'enzyme étant intracellulaire, d'autres, toutefois, réfutent l'idée que ces anticorps soient directement impliqués dans la genèse des crises épileptiques de ces patients, et pensent que leur présence ne représente qu'un épiphénomène d'une autre affection sous-jacente [31, 32]. Les cas pédiatriques restent rares [33 - 36], et comme chez l'adulte, semblent être particulièrement résistants à toute forme d'approche thérapeutique, y compris immune.

Encéphalite de Rasmussen

L'encéphalite de Rasmussen est caractérisée par une hémiatrophie cérébrale progressive, entraînant une hémiparésie contralatérale, une épilepsie réfractaire avec crises focales pouvant prendre la forme d'une épilepsie partielle continue (EPC), et des difficultés cognitives [37]. Elle se manifeste typiquement dans l'enfance, même si un début tardif a été rapporté chez certains patients. Les études histopathologiques du tissu cérébral de patients en étant atteints montrent diverses modifications inflammatoires, dont l'origine semble être une réaction anormale de cellules T cytotoxiques contre les neurones et les astrocytes, sous l'influence du Granzyme B [37, 38]. Les nombreux arguments en faveur d'une dysfonction immunitaire dans cette entité incluent également la présence de certains autoanticorps sériques ou intrathécaux dirigés contre divers types ou sous-unités des récepteurs glutamatergiques [37, 39], même si le rôle de la réponse humorale dans cette entité est très controversé, et des valeurs élevées d'immunoglobulines G, de lymphocytes T CD4+, de TNF alpha et de Granzyme B dans le LCR de certains patients [40]. Les bases étiologiques et les éventuels facteurs déclenchants de cette entité restent à éclaircir. Sur le plan thérapeutique, diverses thérapies immunes à long-terme, incluant immunoglobulines intraveineuses, stéroïdes, anticorps monoclonaux et tacrolimus, peuvent aider [38, 41, 42]. Les molécules anti-épileptiques classiques n'apportent aucun contrôle sur les crises, et une approche chirurgicale (hémisphérectomie) doit être envisagée précocement dans ce type de situation.

Syndrome épileptique lié à une infection fébrile (FIRES)

Le syndrome épileptique lié à une infection fébrile (« febrile infection-related epilepsy syndrome », FIRES) se manifeste initialement par des crises répétées ou un état de mal épileptique extrêmement prolongé, potentiellement létal, au décours d'un état infectieux fébrile [43]. Les enfants atteints présentent typiquement par la suite une épilepsie réfractaire et des troubles cognitifs sévères. Les acronymes suivants ont été proposés pour décrire des tableaux cliniques similaires, dont l'expression clinique pourrait être dépendante de la maturation cérébrale [44]: AERRPS, pour « acute encephalitis with refractory, repetitive partial seizures » [45, 46]; NORSE, pour « new-onset refractory status epilepticus » [47]; ou encore DESC, pour « devastating encephalopathy in school-age children » [48]. L'étiologie de cette entité reste inconnue. Les analyses de laboratoire effectuées écartent toute forme d'infection sous-jacente. Diverses hypothèses dysimmunes, mitochondriales et génétiques ont été soulevées dans certaines publications récentes [43, 44, 49]. Sur le plan immun, la présence d'autoanticorps a été mise en évidence dans le sérum ou le LCR de certains patients. Les cibles de ces derniers incluaient la décarboxylase de l'acide glutamique (GAD), le noyau cellulaire, la gylcoprotéine bêta-2, le muscle lisse, la cardiolipine, la neuropile, le VGKC, ou encore le récepteur au glutamate de type 3 (GLUR-3) [43, 50 - 54]. Les rares observations histopathologiques publiées ne montrent pas d'atteinte inflammatoire spécifique du système nerveux central, toutefois [43].

Certains auteurs pensent que le syndrome IHHS (pour « idiopathic hemiconvulsion-hemiplegia syndrome »), associant des hémiconvulsions suivies d'une hémiplégie et souvent d'une épilepsie réfractaire, fait partie d'un même spectre d'encéphalopathies aiguës avec état de mal médié par l'inflammation (AEIMSE) [44, 55, 56], et que toutes ces entités devraient être regroupées sous ce dernier terme.

Diverses approches thérapeutiques immunomodulatrices aggressives et précoces peuvent parfois améliorer le pronostic de ces entités complexes [44, 57], qui restent toutefois exceptionnellement difficiles à traiter dans la majorité des cas.

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Autoimmune Epilepsies: Treatment Overview

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Summary

Seizure and status epilepticus may be related to antibody mediated autoimmune encephalitides. Prompt recognition of these disorders is mandatory to offer the patient adapted therapeutic options. Associated antibodies can be classified according the cellular location of the target antigen. Work-up, including specific tumour screening, prognosis and therapeutics are directly related to the considered antibody. Onconeuronal antibodies are highly associated with an underlying tumour and response to immunotherapy is disappointing. Immunomodulation for intracellular synaptic antigens antibodies associated disorders may offer a favourable outcome. Cell-surface synaptic antigens antibodies are less likely associated to an underlying tumour and response to immunotherapy may be excellent. Cancer therapy, if applicable, is crucial. First line immunotherapy should be offered to all patients with seizure or status epilepticus related to autoimmune encephalitides. Second line immunomodulation should be discussed in selected patients with cell-surface antigens antibodies.

Epileptologie 2014; 31: 32 – 38

Key words: Seizure, paraneoplastic neurological syndromes, autoimmune encephalitides, autoantibodies, intracellular antigens, cell-surface synaptic antigens, immunomodulation

Epilepsies autoimmunes : Revue thérapeutique

Les crises d'épilepsie et l'état de mal épileptique peuvent être liés à des encéphalites auto-immunes. La reconnaissance rapide de ces troubles est importante afin de proposer au patient des options thérapeutiques adaptées. Les anticorps associés peuvent être classés selon la localisation cellulaire de l'antigène cible. Le bilan à effectuer, incluant la recherche spécifique d'une tumeur, le pronostic et la thérapeutique, sont directement liés à l'anticorps considérés. Les anticorps onconeuronaux sont fortement associés à une tumeur sous-jacente et la réponse à l'immunothérapie est souvent décevante. L'immunomodulation concernant les syndromes associés à des anticorps dirigés contre des antigènes intracellulaires synaptiques peut offrir une issue favorable. Les anticorps dirigés contre des antigènes synaptiques de surface cellulaire sont moins susceptibles d'être associées à une tumeur sous-jacente et la réponse à l'immunothérapie peut être excellente. Le traitement du cancer est cependant crucial. Une première ligne d'immunothérapie doit être offerte à tous les patients présentant des crises d'épilepsies ou un état de mal épileptique liés à une encéphalite auto-immune. Une deuxième ligne d'immunosuppression doit être systématiquement discutée chez les patients présentant des anticorps dirigés contre des antigènes de surface cellulaire.

Mots clés : Crises, syndromes paranéoplastiques neurologiques, encéphalites autoimmunes, autoanticorps, antigènes intracellulaires, antigènes de surface cellulaire synaptiques, immunomodulation

Autoimmune Epilepsien: Therapieübersicht

Epileptische Anfälle und Status epilepticus können mit autoimmunen Enzephalitiden zusammenhängen. Eine rasche Erkennung dieser Störungen ist Voraussetzung für eine angemessene Behandlung. Die entsprechenden Antikörper können nach der zellulären Lage des Zielantigens klassifiziert werden. Untersuchungen, einschliesslich der Suche nach einem Tumor, Prognose und therapeutische Massnahmen hängen direkt mit dem betreffenden Antikörper zusammen. Die onkoneuronalen Antikörper sind stark verbunden mit einem zugrundeliegenden Tumor und die Reaktion auf Immuntherapie ist enttäuschend. Immunmodulation betreffend diejenigen Syndrome, die mit gegen intrazelluläre synaptische Antigene gerichteten Antikörpern zu tun

haben, könnte günstige Auswirkungen haben. Bei Antikörpern, die sich gegen synaptische, sich auf der Zelloberfläche befindliche Antigene richten, ist es weniger wahrscheinlich, dass sie mit einem Tumor in Verbindung gebracht werden können, und die Immuntherapie kann hervorragend sein. Die Krebsbehandlung ist auf jeden Fall zentral. Bei Patienten mit epileptischen Anfällen oder Status epilepticus verbunden mit einer autoimmunen Enzephalitis sollte in erster Linie eine Immuntherapie angeboten werden. In zweiter Linie sollte bei Patienten mit gegen auf der Zelloberfläche liegenden Antigenen gerichteten Antikörpern systematisch über eine Immunsuppression diskutiert werden.

Schlüsselwörter: Anfälle, paraneoplastische neurologische Syndrome, autoimmune Enzephalitiden, Autoantikörper, intrazelluläre Antigene, synaptische zelloberflächliche Antigene, Immunmodulation

Introduction

Autoimmune encephalitides are immune mediated disorders of potential paraneoplastic origin. Seizures and status epilepticus are frequently encountered in such diseases. Recent discoveries of new antibodies changed drastically the concept of autoimmune encephalitides. From a rare and almost strictly paraneoplastic disorder with poor outcome and no response to treatments, the current definition now considers antibody-mediated diseases with good prognosis and striking response to immunotherapy. The former was associated to the so-called onconeuronal antibodies, the later with cell-surface antigen antibodies. Based on the antigen cellular location, three groups can be constituted [1]: intracellular, synaptic and cell-surface antigens targeting antibodies. Antibodies from the same group share common features, such as pathophysiology, association with tumour and response to immunotherapy. Despite the presence of one of these antibodies almost always signs the immune origin of a disorder, the absence of such markers should not rule out that etiology [2]. The present review (partially adapted from [3]) will cover only the antibodies associated to seizures related to autoimmune encephalitides and will focus on treatment evidence.

Group 1: nuclear and cytoplasmic neuronal antigens antibodies (NCNA-Abs)

Onconeuronal antibodies (ONA) targeting intracellular cytoplasmic antigens are associated with seizures and encephalitides and consist of anti-Hu (Hu-Abs), anti-Ma2 (Ma2-Abs) and anti-CV2/CRMP5 antibodies (CV2/CRMP5-Abs). These diseases are rather rare: a multicentric European study conducted during 8 years was able to compile less than 1000 cases and incidence is estimated being about 0.01% of all cancers [4]. Most are of paraneoplastic origin and the nature of the antibody may suggest a specific type of underlying tumour. Hu-Abs are heavily related to small cell lung carcinoma (SCLC) [4], Ma2-Abs to testicular seminoma [5] and CV2/CRMP5-Abs with SCLC or malignant thymoma [6]. The exact function of these antibodies is still under debate. Neither the injection of antibodies [7, 8], nor the immunisation of murine model with purified HuD antigens [8], nor the injection of activated T-cells against Yo or Hu antigens [8] recreated the clinical pattern. These antibodies may be simple markers of a cytotoxic T-cell immune response directed towards neurons [7]. Indeed, because of neuronal loss, complete recovery is not reachable and the main therapeutic purpose is to stabilise the neurological symptoms.

Considering the rarity of these disorders, only few clinical trials are available. Most included patients with diverse neurological patterns and antibodies. The treatment corner stone of patients with NCNA-Abs consists on tumour cure. Aggressive cancer therapy should be initiated as soon as possible and poor clinical status should not be an obstacle to surgery and chemotherapy in paraneoplastic neurological syndromes. The quest for a tumour should be oriented by the nature of the antibody. Surgery or chemotherapy alone may, very infrequently, offer good clinical outcome [9]. Immunotherapy may play a minor role. Retrospective clinical trials including patients with Hu-, CV2- or Ma2-Abs are presented in **Table 1**. One prospective study concluded that aggressive immunotherapy (with cyclophosphamide) should be proposed [10]. The other prospective study [11] using non-conventional medication was disappointing. Response to immunotherapy is generally poor, likely because of neuronal loss. However, sparse cases have been reported with a favourable outcome. Corticoids may have a slight effect on outcome [12, 13]; intravenous immunoglobulins (ivIg) are generally not highly efficient, however in a very small proportion of patients, a favourable response has been observed [14]; plasma exchange may be as ineffective as ivIg [15]. Cyclophosphamide, in association with corticoids and ivIg, may offer a “useful stabilisation” in patients with Hu-Abs [16]. Few patients on rituximab showed a favourable evolution [17], but data are lacking. Tacrolimus in patients with Hu-Abs may improve neurological deficits and is well tolerated [18]. The best option to improve outcome of patients with NCNA-Abs seems to treat as soon as possible the underlying cancer to stop the immune reaction and the neuronal death [16, 19]. According to the relative safety of first-line immunotherapy and a rather small benefit, first line immunotherapy (corticoids, ivIg or PE) should always be proposed. Cyclophosphamide should be administred as a second line immunotherapy inselected patients.

Table 1: Main treatment studies in Group 1 antibodies (NCNA-Abs). (Adapted from [3])

Type of study	Antibodies	Number of patients	Treatment modalities	Conclusions
Retrospective	Hu and Yo [20]	21	ivIg	Mostly stabilisation of neurological symptoms
	Hu, Yo and CV2 [16]	16	ivIg, corticoids, cyclophosphamide	Mostly stabilisation of neurological symptoms
	Yo [21]	19	Immunomodulation (not specified)	No improvement
	Hu [22]	200	ivIg, corticoids, cyclophosphamide, PE	Infrequent clinical improvement
	Hu [23]	73	Corticoids, ivIg, cyclophosphamide, azathioprine	Infrequent clinical improvement
	Yo, Hu, DNER and Ri [24]	48	Tumour treatment, immunosuppression	Few patients improved after tumour therapy
	Ma2 [5]	38	Tumour therapy if applicable, immunotherapy	A third of patients with favourable outcome and 50% with clinical degradation
	Hu and Yo [17]	9	Rituximab	4/9 with clinical improvement
	Hu, Yo and CV2 [18]	26	Tacrolimus	Few clinical improvement
Prospective	Hu, Yo, CV2 [10]	20	PE and cyclophosphamide versus PE and chemotherapy	Better outcome in patients treated with cyclophosphamide
	Hu [11]	15	hCG	A third of patients harboured a significant improvement

hCG: human chorionic gonadotropin, ivIg: intravenous immunoglobulin, PE: plasma exchanges.

Group 2: intracellular synaptic antigens antibodies (ISA-Abs)

Antibodies targeting intracellular synaptic antigens include anti-GAD65 (GAD65-Abs) and anti-amphiphysin antibodies (Amphiphysin-Abs) [1]. Both antigens are located within the presynaptic terminal of neurones, a region where antibodies can reach cytoplasmic proteins. Conversely to NCNA-Abs, injections of GAD65- or Amphiphysin-Abs from patients induce similar clinical patterns in rodents [25]. Thus, it is suggested that humoral immune response may also be part of the pathological process.

Most of the patients with GAD65-Abs suffer from stiff-person syndrome (SPS) and cerebellar dysfunction [26]. Seizures are infrequent, however some cases report limbic encephalitis and refractory epilepsy [27]. $GABA_B$R-Abs may be associated in about 10% of cases [28]. Paraneoplastic origin is infrequent with GAD65-Abs, accounting for around 5% of cases, but should be highly suspected with Amphiphysin-Abs (breast carcinomas and SCLC). Within patients with seizure or limbic encephalitis in association to GAD65-Abs, response to immunotherapy is inconsistent [27]. However, rituximab [29] or azathioprine [29] in seizure related GAD65-Abs encephalitis and cyclophosphamide may be effective in status epilepticus with GAD65-Abs [30, 31]. Sparse observations concluded on a favourable outcome in Amphiphysin-Abs SPS with immunotherapy (corticoids and ivIg) [32].

Group 3: cell-surface synaptic antigens antibodies (CSSA-Abs)

Seizure-associated antibodies will be specifically discussed in this section. They consist, in order of frequency, of antibodies targeting cell-surface proteins such as N-methyl-D-aspartate receptor (NMDAr [33]), Leucine-rich, glioma inactivated 1 (Lgi1 [34, 35]),

Table 2: Main treatment studies in Group 3 antibodies (ISA-Abs). (Adapted from [3])

Type of study	Antibodies	Number of patients	Treatment modalities	Conclusions
Retrospective	GAD65 and amphiphysin	79	Benzodiazepines, corticoids, ivIg, azathioprine, MM, cyclophosphamide	PERM syndrome harbours a poor outcome despite immunotherapy
	GAD65 [27]	9	Corticoids	None became seizure free
Prospective	GAD65 [36]	16	ivIg versus placebo	Significant improvement after immunotherapy

ivIg: intravenous immunoglobulin, MM: mycophenolate mofetil, PERM: progressive encephalomyelitis with rigidity and myoclonus.

Contactin-associated protein 2 (Caspr2 [35, 37]), gamma amino butyric acid (B) receptor ($GABA_BR$ [28, 38]), alpha-amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid receptor (AMPAr [39]), glycine receptor (GlycineR [40]), metabotropic glutamate receptor 5 (mGluR5 [41]) and dipeptidyl-peptidase-like protein-6 (DPPX [42]). These antibodies share common specificities: they all may have a pathogenic role, act by disrupting the cross-talk between the targeted antigen and other proteins, are responsible for immunotherapy-highly-responsive disorders – much commonly than with other antibodies, and are overall of rare paraneoplastic origin. Most data on treatment come from few clinical studies and cases reports. No prospective study is nowadays available.

Anti-NMDAr antibodies (*NMDAr-Abs*) Classically, patients with **NMDAr-Abs** are young women with psychiatric symptoms at onset, rapidly followed by seizure – in about 70% of cases [43], movement disorders, dysautonomia, central hypoventilation and cognitive alterations. Sixty per cent of female patients have an underlying ovarian teratoma [33]. Children and male may also be affected, but in a rather lesser extent and disease is rarely associated with a tumour [44]. Clinical pattern may differ within male and children patients, essentially at onset, with a higher tendency to harbour partial seizures or status epilepticus. Following symptoms and complete clinical pattern are however similar to female patients. Favourable response to treatment is high, in about 75% of cases. Disease should be recognized promptly and surgery (when appropriate) with concomitant first line immunotherapy (corticoids and ivIg) performed. Sparse data on favourable outcome after surgery alone for ovarian teratoma [45] should not delay immunotherapy. If response is poor, a second line immunotherapy (rituximab, cyclophosphamide) should be administered. Response to second line immunotherapy may be particular slow within patients who did not show signs of improvement after first line immunotherapy [46]. Long term immunomodulation, obtained with mycophenolate mofetil or azathioprine, should be offered to avoid relapse [46], but duration of treatment is not clear. A clinical trial on treatment of NMDAr-Abs is now running using immunotherapy with rituximab (NIH, Principal investigators: A. Nath and J. Dalmau) [1].

Anti-voltage gated potassium channels complex antibodies (Lgi1- and Caspr2-Abs) Antibodies targeting proteins from the VGKC complex can be segregated in three groups, depending on the antigen they interact with. Lgi1- [34, 35] and Caspr2- [35, 37] are two well described antigens. Other specific targets may also coexist but have not been identified so far: patients CSF may show immunoreactivity towards VGKC complex, however without reactivity against the aforementioned target antigens [47]. Pathophysiological role, clinical relevance and association with a tumour may vary according to the considered antibody.

Lgi1-Abs are related to limbic encephalitis with prominent amnesic syndrome and seizure, affecting elderly patients. Faciobrachial dystonic seizures à *bascule* are almost pathognomonic [48]. Hyponatremia is often present. Lgi1-Abs target a secreted protein and disrupt the ligand-receptor interaction between Lgi1 and ADAM22, leading to a reduction of synaptic AMPAr [49]. Tumour is infrequently encountered, in less than 10% of patients. Sparse observations are available, however immunotherapy (corticoids, ivIg, PE, rituximab, cyclophosphamide, cyclosporine) seems to be efficient in most patients [34, 35].

Patients with **Caspr2-Abs** may present with nerve terminal hyperexcitability (Isaacs' syndrome), central nervous diseases (encephalitis) or a conjunction of both (Morvan syndrome) [36]. Function of Caspr2 is still unclear however it may play a role in potassium channel function. Paraneoplastic cases are more frequent affecting about 30% of patients (malignant thymoma). Paraneoplastic cases evolution is less favourable than dysimmune cases despite aggressive treatment. Favourable outcome may be obtained with immunotherapy (corticoids, ivIg, PE, rituximab, cyclophosphamide and cyclosporine) [35, 37].

Anti-$GABA_BR$ antibodies ($GABA_BR$-Abs) **$GABA_BR$-Abs** may be found within patients with limbic ence-

Table 3: Main treatment studies in Group 2 antibodies (CSSA-Abs). (Adapted from [3])

Type of study	Antibodies	Number of patients	Treatment modalities	Conclusions
Retrospective	AMPAr [39]	10	Tumour treatment if applicable, corticoids, PE, ivIg, azathioprine	Mostly favourable outcome
	Lgi1 [34]	57	Corticoids, ivIg, PE, azathioprine, rituximab, cyclosporine	Favourable outcome in 78% of patients
	Lgi1 and Caspr2 [35]	96	Corticoids, ivIg	Favourable outcome in patients with Lgi1 and anti-Caspr2 without associated tumour
	$GABA_BR$ [28]	15	Tumour surgery and chemotherapy if applicable, corticoids, ivIg, PE, cyclosporine, rituximab	Favourable outcome in most patients
	NMDAr [33]	>500	Corticoids, ivIg, PE, rituximab, cyclophos-phamide, MM	Favourable outcome in about 75% of cases
	Caspr2 [37]	8	Tumour surgery if applicable, corticoids, ivIg, PE, cyclosporine, rituximab	Most patients responded to immunotherapy
	mGluR5 [41]	9	ivIg	Significant improvement in muscle strength but not in CMAP amplitude
	$GABA_BR$ [38]	20	Tumour surgery and chemotherapy if applicable, corticoids, ivIg	Favourable outcome or stabilisation in 7 patients on 10
	GlyR [40]	9	Chemotherapy, corticoids, ivIg, PE, azathioprine, benzodiazepine, baclofen	Improvement in the majority of cases

ivIg: intravenous immunoglobulin, MM: mycophenolate mofetil, PE: plasma exchanges.
CMAP: compound muscle action potential

phalitis and prominent temporal lobe seizure or status epilepticus, mostly refractory to medical treatment [38]. Underlying mechanism is not clear. In about 50% of patients, a tumour is found [28, 38]. More than half of described patients responded well to treatment, consisting on the association of chemotherapy, when applicable, and immunomodulation (mostly ivIg and PE) [28, 38].

Anti-AMPAr antibodies (AMPAr-Abs) **AMPAr-Abs** are associated with limbic encephalitis and seizures are rare. Most patients harbour an underlying tumour (malignant thymoma, breast cancer or SCLC). Response to immunotherapy (corticoids, PE, ivIg, azathioprine) and surgery, when applicable, is rather good but patients may relapse and harbour persistent cognitive dysfunction [39].

Anti-GlycineR antibodies (GlyR-Abs) Only few patients with **GlyR-Abs** have been so far reported. Most patients have a SPS and some may harbour PERM (progressive encephalomyelitis with rigidity and myoclonus). A cancer is rarely associated [40]. The exact role of these Abs is still unknown. SPS are treated first with GABAergic drugs and prognosis can be fairly good. Immunotherapy offers good outcome in most patients with SPS [40], less with PERM.

Anti-mGluR5 antibodies (mGluR5-Abs) **mGluR5-Abs** have been reported in two patients with Ophelia syndrome in association to Hodgkin's lymphoma (HL). Cases reported showed favourable outcome after HL chemotherapy and iv corticoids, or mediastinal radiotherapy alone [41].

Anti-DPPX antibodies (DPPX-Abs) Four patients with **DPPX-Abs** have been reported so far, 3 presented seizure or status epilepticus, in association with cognitive failure and psychiatric features [42]. Immunotherapy (corticoids, ivIg and rituximab) offered good outcome in 3 patients.

Paediatric concerns

Seizures related to autoimmune encephalitides are increasingly being diagnosed in children. Clinical pattern may not radically differ from adult patients. NCNA and ISA-Abs are infrequently encountered in children [50] and most cases related to CSSA-Abs are not of paraneoplastic origin. However, NMDAr-Abs positivity should lead to ovarian teratoma screening. Treatment in children should be as aggressive as in adult patients. Second line immunotherapy should be started if first line failed. On a recent paper [51], it is suggested to start, in case of suspected or proven autoimmune encephalitis associated seizures, with intravenous corticoids, rapidly followed by ivIg. If awaited response is not reached, plasma exchange or new ivIg administration is suggested. Patients who fail to respond should be switched to second line immunotherapy, i.e. rituximab or cyclophosphamide.

Conclusions

Treatment of seizures associated to autoimmune encephalitides is a two steps process. Cancer therapy in paraneoplastic neurological disorders is the first step when applicable and should be associated with prompt onset of medical treatment. First line immunotherapy (corticoids, ivIg, PE) can be administered to virtually all patients – considering the possible benefit and with high safety, independently of the nature of the targeted antigens. Cyclophosphamide and rituximab (second line immunotherapy) should be proposed to selected patients. The efficiency of immunotherapy is disappointing in patients with NCNA-Abs, fairly good in patients with ISA-Abs and excellent in patients with CSSA-Abs.

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Imaging of Autoimmune Epilepsies

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Abbreviations:

CSF:	Cerebrospinal fluid
CT:	Computed tomography
DTI :	Diffusion tensor imaging
FDG :	18F-fluorodeoxyglucose
FLAIR :	Fluid-attenuated inversion recovery
HE :	Hashimoto encephalitis
HHV6 :	Human herpes virus 6
GET2 :	Gradient echo T2
MRI :	Magnetic resonance imaging
MRS :	Magnetic resonance spectroscopy
PNLE :	Paraneoplastic limbic encephalitis
SWI :	Susceptibility weighted imaging
VGKC-Ab:	Voltage-gated potassium channels antibodies

Summary

Epilepsy due to an autoimmune disease is a recently recognized entity. Among the best-known diseases are paraneoplastic limbic encephalitis, limbic encephalitis associated with voltage-gated potassium channels (VGKC)) antibody glutamic acid decarboxylase antacid, antireceptor antibodies N-methyl-D-aspartate, Rasmussen and Hashimoto encephalitis.

More efficient imaging technics and immunologic laboratory analyses have allowed us to deepen our knowledge concerning these diseases that are most common in adults.

In this article we will describe the most common imagery findings and the most appropriate methods of image analysis.

Epileptologie 2014; 31: 39 – 43

Key words: epilepsy, MRI, autoimmune diseases, paraneoplastic encephalitis, voltage-gated potassium channels encephalopathy, anti GAD

Imagerie des épilepsies auto-immunes

L'épilepsie causée par une maladie auto-immune est une entité récemment reconnue. Les étiologies les plus fréquentes sont l'encéphalite limbique paranéoplasique, l'encéphalite limbique associée à l'anticorps anticanaux potassiques voltage dépendant, l'encéphalite à anticorps antiacide glutamique decarboxylase, l'encéphalite à anticorps antirécepteur du N-methyl-D-aspartate, l'encéphalite de Rasmussen et l'encéphalite de Hashimoto.

Ces maladies sont rares et méconnues. Les avancées techniques en imagerie et en laboratoire nous ont permis d'approfondir nos connaissances.

Dans cet article, nous allons décrire les anomalies radiologiques les plus souvent rencontrées dans chaque maladie ainsi que les méthodes d'imagerie les plus adaptées pour leur analyse.

Mots clés : Epilepsie, IRM, maladies autoimmunes, encéphalite paranéoplasique, encéphalopathie canaux potassiques voltage-dépendant, anti AGD

Bildgebung der autoimmunen Epilepsien

Durch Autoimmunerkrankungen verursachte Epilepsien stellen eine erst seit kurzem bekannte Entität dar. Die häufigsten Ursachen sind die paraneoplastische limbische Enzephalitis, die limbische Enzephalitis mit gegen spannungsabhängige Kaliumkanäle gerichteten Antikörpern, die Enzephalitis mit Anti-Glutamatdecarboxylase-Antikörpern, die Enzephalitis mit Antikörpern gegen N-Methyl-Aspartatrezeptoren, die Rasmussen-Enzephalitis sowie die Hashimoto-Enzephalitis.

Es handelt sich hierbei um seltene und wenig bekannte Erkrankungen. Fortschritte in der Bildgebung und in Labortechniken haben es jedoch ermöglicht, unsere Kenntnisse zu erweitern. In dieser Arbeit werden die häufigsten radiologischen Befunde obengenannter Autoimmunerkrankungen beschrieben, mit Empfeh-

lungen zur Optimierung der Bildgebungstechnik.

Schlüsselwörter: Epilepsie, MRI, Autoimmunerkrankungen, paraneoplastische Enzephalitis, Enzephalitis mit gegen spannungsabhängige Kaliumkanäle gerichteten Antikörpern, Anti-GDA

Introduction

In this paper we will describe the most frequent findings detected by imagery in autoimmune diseases associated with epilepsy.

The imaging technic of choice is resonance magnetic imaging (MRI), we will describe the most adequate technical protocols as well as the anomalies found in these diseases.

Imagery and autoimmune laboratory studies play a key role in the diagnosis and follow up.

Imaging technic

The imagery of choice is magnetic resonance imaging (MRI) at 3T using a 32 channel brain coil, the technical protocol recommend is: coronal fast spin echo T2 (FSET2), repetition time (TR) 7520 ms; echo time (TE) 114 ms; voxel size 0.5 × 0.4 × slice thickness 3 mm, the position of the slices is perpendicular to the hippocampi as well as in the axial plane, 3D Fluid inversion recovery(FLAIR) TR 5000; TE 419; inversion time (TI) 1800; isotropic voxel size 0.9 × 0.9 × 0.9 mm (**Figure 1**), diffusion tensor imaging (DTI) TR 8000 ms; TE 84 ms, 30 directions, arterial spin labeling (ASL) TR 4000 ms; TE 12, voxel size 3.4 x 3.4 x slice thickness 4 mm and spin echo (SE) T1 before and after contrast medium and 3DT1 after contrast medium, TR 1750 ms; TE 2.29 ms; isotropic voxel size 0.7 × 0.7 x 0.7 mm [1].

The use of contrast medium is recommended.

The gradient echo T2 (GET2) TE 20 ms, TR 832 ms, slice thickness 4 mm or susceptibility weighted imaging (SWI) are helpful particularly in limbic paraneoplastic encephalitis and limbic encephalitis associated with voltage-gated potassium channels where microbleeds are common.

Computed tomography (CT) is usually realized in the emergency room upon patient arrival but does not allow the diagnosis of this type of epilepsy as the hippocampal abnormalities are difficult to analyze and detection of microbleeds is limited.

Whole PET-F-fluorodeoxyglucose (FDG) is used for detecting malignances in patients where a paraneoplastic encephalitis is suspected.

Paraneoplastic limbic encephalitis (PNLE)

Paraneoplastic limbic encephalitis is a rare disorder affecting 1% of patients with a systemic cancer [2]. It was first described in 1960 by Brierley [3], incidence in males or females depends on the type of tumor implicated. It is characterized by memory loss, personality changes, seizures and dementia.

Around 60% of patients with PNLE have antineural antibodies in the serum or CSF [4].

Anomalies of the hippocampi and limbic system are detected by MRI, hyperintensities on FLAIR/T2 in both or one of the temporal lobes and hippocampi, the inferior frontal region, the insular cortex and cingulate gyrus can also be affected. The symptoms and imaging anomalies appear frequently before detection of the primary neoplastic disease.

The imaging of choice for analysis of these anomalies is MRI.

The most common antibodies associated are the:

- Anti-Hu: associated with small-cell carcinoma of the lungs, the most common cause of paraneoplastic limbic encephalitis (**Figure 2**)
- Anti-Ta: associated with tumors of the testis
- Anti-Yo: associated with breast and ovarian cancers
- Anti-NMDAR: associated with tumors of the ovaries, frequently teratomas
- Anti-CRMP5 (anti-CV2): associated with small-cell carcinoma of the lungs and thymoma
- Anti-Tr: associated with Hodgkin disease

The common MRI findings are hyperintensities and enlarged hippocampi and amygdala in FLAIR and FSE T2 in the early stages of disease followed by atrophy (**Figure 2**). These anomalies may extend to the striatum and thalamus, the brainstem and the cerebellar peduncles. Microbleeds are rare and enhancement is some-

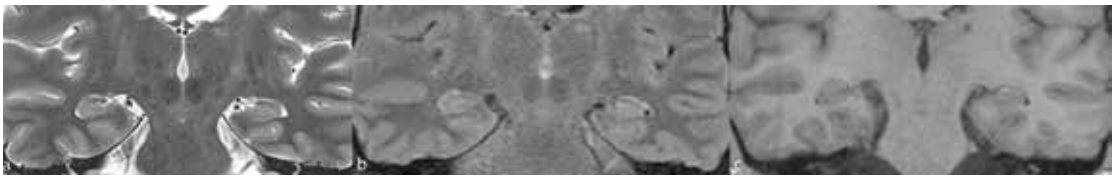

Figure 1: Normal hippocampus on coronal FST2, FLAIR and T1 weighted images (a, b, c)

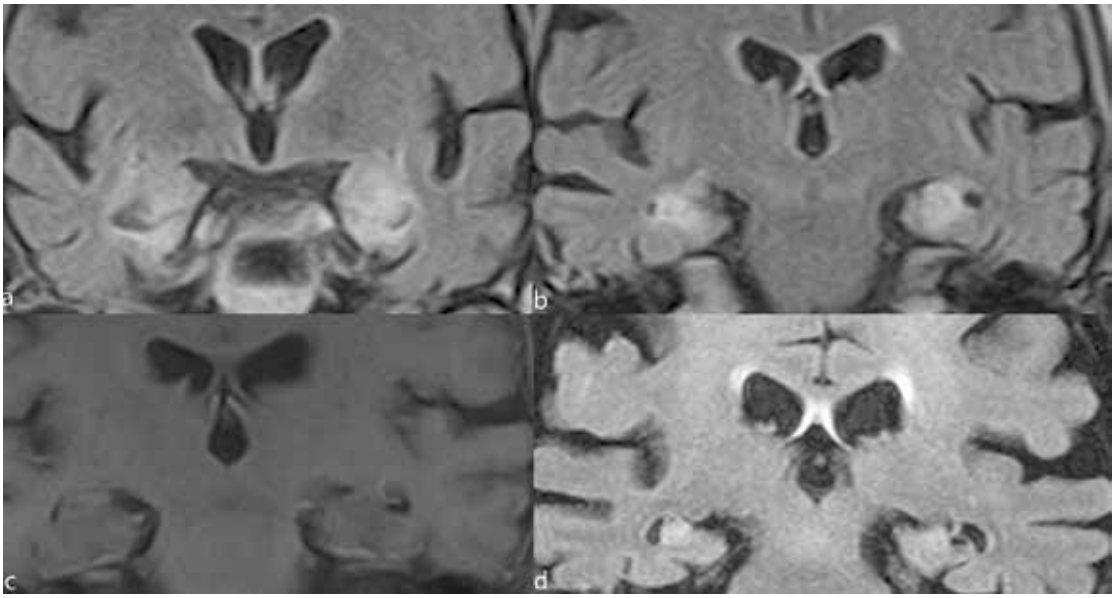

Figure 2: Paraneoplastic encephalitis: 82 year-old woman with carcinoma of the lung, note the hyperintense and enlarged hippocampi and amygdala on T2 (a, b). No enhancement is noted in (c), follow-up 8 months later shows an atrophy of the hippocampi (d).

times associated.

The differential diagnosis of imaging findings includes the human herpes virus 6 (HHV6) [5] encephalitis and other non-paraneoplastic encephalitis such as voltage-gated potassium channel antibody encephalitis, bilateral glioma and gliomatosis cerebri.

Isolated involvement of the pulvinar nuclei may open the differential diagnostic with Creutzfeldt-Jakob disease [6].

The anomalies may regress in the early stages if the primary tumor is removed but often this is not possible due to advanced malignant and infiltrative disease [7].

Whole body PET-18 F-fluorodeoxyglucose (FDG) is used for detecting malignances but is rarely used at the level of the brain. However, non-specific medial temporal and extra-temporal hypermetabolism can be observed in patients with autoimmune epilepsy in the earlier phases [7], and a diminution of intake of FDG in the most advanced phases [7, 8].

Voltage-gated potassium channels antibodies encephalitis (VGKC-Ab)

Voltage-gated potassium channels antibodies disease is an autoimmune non-paraneoplastic reversible limbic encephalitis characterized by memory loss, confusion and seizures.

The imagery is indistinguishable from paraneoplastic encephalitis in the early stages when only the hippocampi and amygdala are affected. They appear hyperintense on T2 and FLAIR and are enlarged in the early stages of disease followed by atrophy [9]. Findings can be unilateral or bilateral (**Figure 3**). A restriction of diffusion can be observed in the same location of the T2/FLAIR anomalies [10] and enhancement can be seen.

Microbleeds have been described in this pathology [9]. A generalized atrophy of the brain is also observed in chronic stages (**Figure 3**).

Findings can be reversible and in some cases this is not treatment dependent.

Normal imaging at the onset is possible.

Treatment includes immunotherapy, plasmapheresis and oral prednisone.

Rasmussen encephalitis

Rasmussen encephalitis is an uncommon progressive encephalitis of unknown cause, however recent research has shown that it is a chronic T-cell mediated disorder [11], with onset in the first decade of life and less common in adults. It is characterized by mental impairment, progressive hemiparesis and drug-resistant epilepsy.

Diagnostic criteria were established in 2005 by Biel et al. [4] and adapted by Olson et al. in 2013 [11] and include clinical symptoms (focal seizures and unilateral cortical deficits) and EEG findings (epileptiform activity and unilateral seizure onset). MRI criteria include hyperintensity of white matter and cortex on FLAIR and

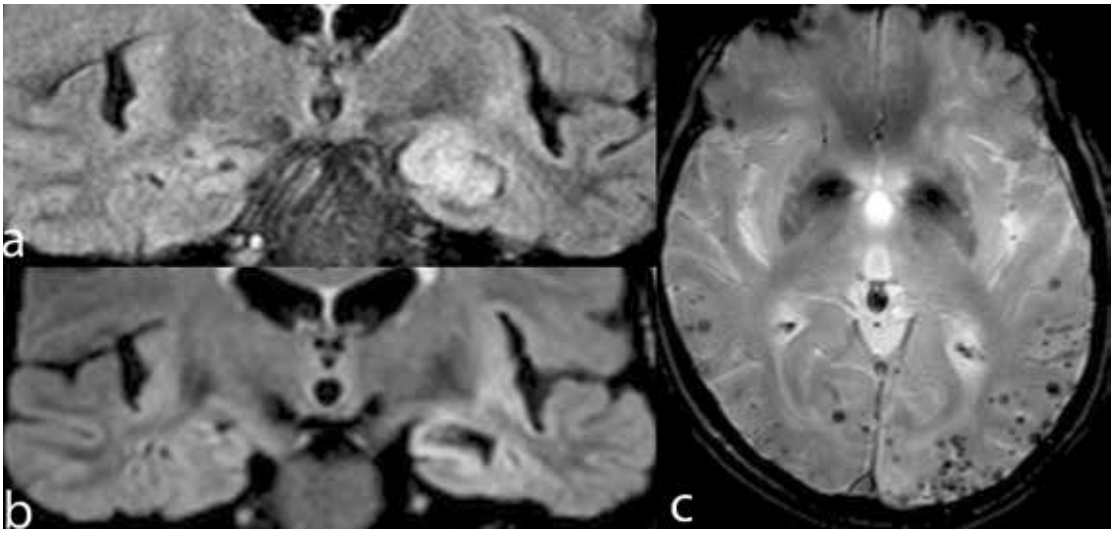

Figure 3: Voltage-gated potassium channels antibodies encephalitis: Coronal FLAIR sequence shows an enlarged left hippocampus (a) observe the atrophy 3 months later associated with diffuse cortical and subcortical microbleeds.

FSET2, unilateral progressive atrophy and no enhancement (**Figures 4, 5**). All of these criteria must be met for the diagnosis as well as 2 of 3 of the following criteria: epilepsia continua or progressive unilateral cortical deficits, progressive unilateral atrophy at MRI and T-cell dominated encephalitis with activated microglial cells.

Pradeep et al. [12] had modified the imaging criteria and proposed 4 stages as follows (**Figures 4, 5**):

Stage 1: swelling of the cortex, with a hyperintense T2/FLAIR signal;
Stage 2: normal volume and hyperintense signal;
Stage 3a: mild atrophy with hyperintense signal;
Stage 3b: moderate atrophy with hyperintense signal; and
Stage 4: severe atrophy with normal signal.

Magnetic resonance spectroscopy (MRS) studies show decreased NAA levels and increased (cho) peaks, resulting in a decreased NAA/cho ratio suggestive of neuronal loss or dysfunction and elevated lactate [12 - 15].

Longo et al. have described a case showing an association between Parry-Romberg and Rasmussen encephalitis [16].

Hashimoto encephalitis

Clinical presentation of Hashimoto encephalopathy is variable and observed in the pediatric, adult, and elderly populations. Common clinical manifestations include stroke-like symptoms, movement disorders, dementia, and focal or generalized seizures. Diagnosis is confirmed by an elevated antithyroid antibody level encephalopathy when other more common infectious, metabolic, and toxic causes of encephalopathy have been completely excluded [17].

Hashimoto encephalitis (HE) presents a wide range of MRI findings such as enlarged and hyperintense unilateral or bilateral hippocampi, transient subcortical ischemia, cortical atrophy, and unilateral cerebral atrophy. Bohnen et al. reported diffuse reversible white matter anomalies that mimic a leukodystrophy and resolve after treatment [18].

In other cases, HE my simulate tumors, granuloma, infection or degenerative disorders [19, 20] however patients may have a normal MR.

Findings in MRS are diverse for example Singh H et al. described a peak of lactate in MR-spectroscopy in the symptomatic phase with a normalization of values with clinical improvement of the patient [21]. Su et al. reported a decrease in N-acetylaspartate (NAA/Cr=1.19) and myo-inositol peaks, and an elevation in lipid, lactate, glutamate/glutamine multiplet and choline (Cho/Cr = 1.21) peaks, which supported a cerebral inflammatory change.

Diverse physiopathologic mechanisms have been proposed such as the role of anti-thyroid antibodies produced intrathecally [22, 23], perivascular lymphocyte infiltration involving leptomeninges and the brain stem, signs of vasculitis, cerebral hypoperfusion, and toxic effects of thyrotropin-releasing hormone.

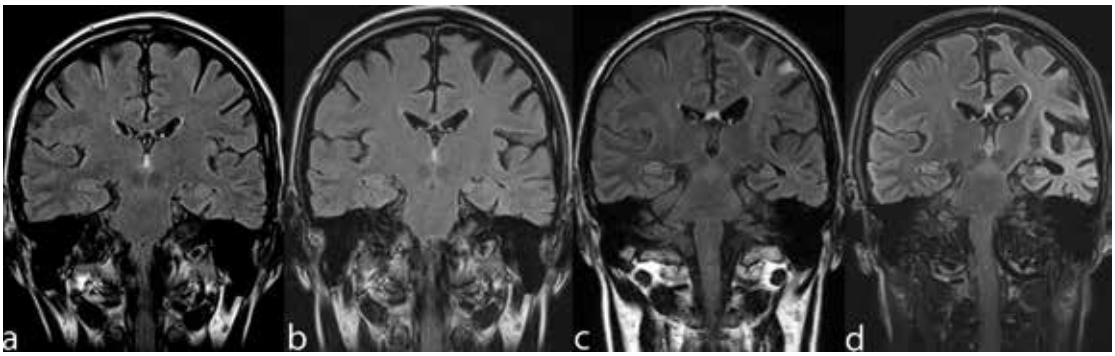

Figure 4: Rasmussen encephalitis: Evolution of this disease is shown on coronal FLAIR MR, in the first control the MRI is normal in 1999 (a). In 2002, left cortical-subcortical atrophy is present.
In 2006, note the high signal of the left frontal lobe and the left hemispheric cortical-subcortical atrophy.

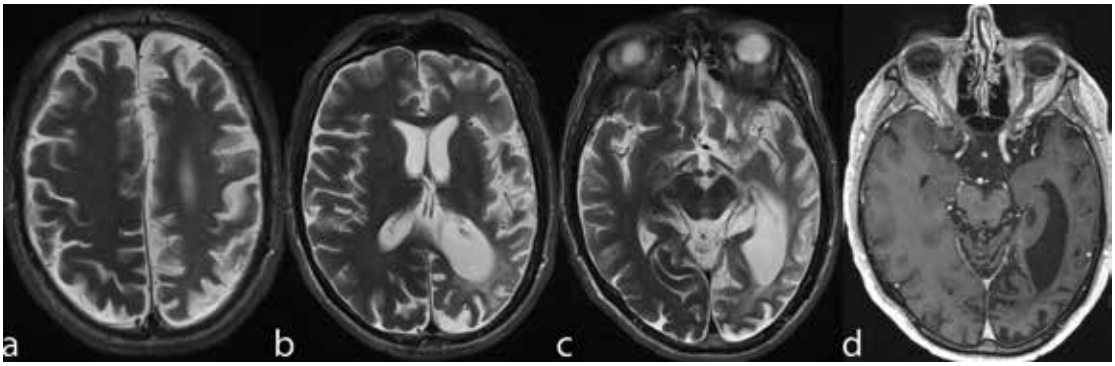

Figure 5: Rasmussen encephalitis: Axial FSE T2 illustrates the last control of this patient in 2013, note the important cortico-subcortical atrophy of the left cerebral hemisphere associated with a diffuse high signal (a, b, c). Enhancement is absent (d).

Anti-N-methyl-D-aspartate-receptor (NMDAR) encephalitis

This entity has been reported in 60% of women with ovarian cancer [24] but recently it has also been identified in infants and adolescents without tumors [25]. NMDARE symptoms in the initial phase include a flu-like illness followed by psychiatric disorders such as psychosis, hallucinations, anxiety, agitation, and paranoia; hyperactivity dominates in children. Altered levels of consciousness, severe dysautonomia, central hypoventilation, orofacial dyskinesias and seizures are common [26].

CT scans of the brain are normal. MRI may also be normal or demonstrate nonspecific anomalies in T2-weighted or FLAIR sequences in the mesial temporal lobes, cerebral cortex, cerebellum, basal ganglia or brainstem. Contrast enhancement is infrequent, a meningeal or cortical enhancement can be observed. In the chronic stage cerebral atrophy can be encountered [24].

Antibodies directed against glutamic acid decarboxylase (anti-GAD)

Anti-GAD is a rare encephalitis characterized by psychiatric symptoms, stiff syndrome, subacute memory loss, and seizures [27] and is potentially partially reversible if the diagnosis is early.

MRI may be normal or can show anomalies implicating the mesial temporal lobe and the hippocampi [27] which are enlarged with a high signal. Follow-up MR shows an atrophy of the hippocampi and of the cerebral parenchyma.

Glutamine and glutamate levels are increased in the region of seizure onset in patients with anti-GAD antibodies compared to the contralateral side or in control subjects leading to atrophy [28].

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Der immunogene Status Epilepticus

Franz Josef Holzer und Margitta Seeck

Zusammenfassung

Der immunogene Status Epilepticus (iSE) ist eine heterogene nosologische Entität, die postuliert, dass ein pathogener immunologischer Prozess durch eine Veränderung des Gleichgewichts zwischen exzitatorischen und inhibitorischen Potenzialen zu einem Status Epilepticus (SE) führen kann, der oft intensivmedizinische Betreuung der Patienten verlangt.

Ätiologisch werden paraneoplastische beziehungsweise autoimmune Mechanismen diskutiert, dem humoralen Bestandteil der adaptativen Immunantwort wird gegenüber dem zellulären der Vorrang gegeben.

Dabei wird aktuell das Augenmerk auf Antikörper gerichtet, die entweder einen Tropismus für die Zellmembran der Neuronen beziehungsweise deren Ionenkanäle oder für intrazelluläre Epitope haben.

Es gibt zurzeit keine randomisierte, kontrollierte Studie, die die Wirksamkeit der immunmodulierenden und antiepileptischen Therapien oder deren Kombination im iSE belegen. Die therapeutischen Ansätze werden aus ähnlichen nosokomialen Entitäten abgeleitet (Status Epilepticus auf der einen Seite, immunogene Enzephalitiden auf der anderen), basieren auf beschreibenden Studien und Expertenmeinungen (Evidenzklasse IV).

Unerwarteterweise geht ein langdauernder Status Epilepticus (Superrefractory Status Epilepticus) nicht unbedingt mit einer schlechten Prognose einher, Verläufe mit restitutio ad integrum sind wiederholt auch nach monatelangem SE beschrieben worden und rechtfertigen geduldige, beharrliche Therapien, auch in der Intensivstation.

Epileptologie 2013; 30: 45 – 48

Schlüsselwörter: Status Epilepticus, Autoimmunität, Enzephalitis, Behandlung, Prognose

L'état de mal épileptique immunogène

L'état de mal épileptique immunogène (EMEI) est une entité nosologique hétérogène émettant l'hypothèse qu'un processus immunologique pathogène peut, par un déséquilibre entre potentiels excitateurs et inhibiteurs, entraîner un état de mal épileptique (EME) nécessitant souvent une prise en charge médicale intensive des patients.

Sur le plan étiologique sont évoqués des mécanismes d'origine paranéoplasique ou auto-immune, avec une priorité donnée à la réponse humorale du système immunitaire adaptatif par rapport à la réponse cellulaire.

L'attention se porte actuellement sur les anticorps ayant un tropisme soit pour la membrane cellulaire des neurones ou leurs canaux ioniques, soit pour des épitopes intracellulaires.

Il n'existe à ce jour aucune étude randomisée contrôlée démontrant l'efficacité des traitements immunomodulateurs et anti-épileptiques ou de leur combinaison dans l'EMEI. Les approches thérapeutiques sont dérivées d'entités nosologiques semblables (état de mal épileptique d'un côté, encéphalites immunogènes de l'autre), sur la base d'études descriptives et d'avis d'experts (niveau IV de preuves).

Contre toute attente, un état de mal épileptique de longue durée (super-réfractaire) ne s'accompagne pas nécessairement d'un mauvais pronostic, des évolutions avec restitutio ad integrum ont été rapportées à plusieurs reprises même après des mois d'EME, et justifient des mesures thérapeutiques patientes et obstinées, même en soins intensifs.

Mots clés: Etat de mal épileptique, autoimmunité, encéphalites, traitement, pronostic

Immunogenic Status Epilepticus

Immunogenic status epilepticus (ISE) is a heterogeneous nosological entity, which postulates that a pathogenic immunological process, through a change in the balance between excitatory and inhibitory potentials, can lead to a status epilepticus (SE), which often demands intensive medical care of the patient.

With regard to aetiology, paraneoplastic or autoimmune mechanisms are discussed, the humoral component of the adaptive immune response is given precedence over the cellular immune response.

In this attention is currently turned towards antibodies, which either have a tropism for the cell membrane of the neurons or their ion channels or have a tropism for intracellular epitopes.

There is currently no randomised, controlled study, which provides evidence for the efficacy of the immunomodulating and antiepileptic treatments or their combination in ISE. The treatment approaches are derived from similar nosological entities (status epilepticus on the one side, immunogenic encephalitis on the other), based on descriptive studies and expert opinions (evidence class IV).

Contrary to expectation, a long-lasting status epilepticus (super-refractory status epilepticus) does not necessarily go hand in hand with a poor prognosis, instances of progress with restitutio ad integrum have also been repeatedly described after SE lasting for months and warrant patient, persevering treatments, also in the intensive care ward.

Key Words: Status Epilepticus, Autoimmunity, Encephalitis, Treatment, Outcome

Abgrenzungen

Unter dem Begriff Status Epilepticus (SE) versteht man einen epileptischen Anfall, der eine bestimmte Dauer überschreitet (je nach Definition üblicherweise zwischen 10 und 30 Minuten) oder eine Anfallsserie, bei der interiktal die normalen Funktionen des ZNS nicht wiedererlangt werden (i.e. üblicherweise das Bewusstsein) [1]. Man unterscheidet zwischen nichtkonvulsivem und konvulsivem SE und zwischen Übergangsformen. Die Diagnose wird klinisch und auf der Basis von epilepsietypischen Potenzialen (ETP) beziehungsweise Anfallsmustern im EEG gestellt.

Krankheiten, die das Immunsystem aktivieren oder von ihm ausgehen, können das ZNS angreifen, zum Beispiel via Entzündungen der Myelinscheiden oder der Gefässwände oder via neuronaler Antikörper, die wiederum zu epileptischen Anfällen und in gewissen Fällen zu einem SE führen können. Seit mehr als 10 Jahren werden autoimmune Mechanismen für gewisse Formen von Epilepsien diskutiert [2] und seit der Entdeckung von spezifischen neuronalen Antikörpern immer genauer beschrieben. Die immunologischen Mechanismen, die zu einer Beeinträchtigung des ZNS führen, sind mannigfaltig, und beinhalten unter anderem eine Veränderung der Permeabilität der Blut-Hirn-Schranke und die Aktivierung des zellulären als auch des humoralen Anteils der adaptativen Immunantwort [3, 4].

Unter einem iSE verstehen wir hier einen SE, bei dem unter Ausschluss anderer Ursachen (zum Beispiel virale oder bakterielle Infekte, vorbestehende epileptische Erkrankung, Elektrolytentgleisungen usw.) der Nachweis von spezifischen Antikörpern im Blut und/oder im Liquor beziehungsweise oligoklonaler Banden auf eine immunogene Ätiologie hinweisen. Die beschriebenen Antikörper sind entweder autoimmuner oder paraneoplastischer Herkunft.

Fliessende Übergänge

Der iSE im Sinne unserer Definition beinhaltet neben kompatiblen klinischen Symptomen ein EEG mit rhythmischen epilepsietypischen Potenzialen (ETP) beziehungsweise Anfallsmustern und den Nachweis von Antikörpern, vorzugsweise im Liquor (nicht obligat), wo oft auch eine Pleiozytose (ebenfalls nicht obligat) festgestellt wird. Damit erfüllt der iSE oft alle Kriterien einer Enzephalitis, zeigt aber zusätzlich noch Anfallsmuster im EEG. Da es sich aber bei den meisten Enzephalitis-Patienten nur um oberflächlich abgeleitete EEGs handelt, mit bekanntlicherweise limitierter Sensibilität für iktale Potenziale in tieferen Hirnanteilen (Hippocampus, Amygdala), kann in Einzelfällen vermutet werden, dass es sich bei gewissen autoimmunen oder paraneoplastischen Enzephalitiden ebenfalls um einen iSE handelt, wenn diese mit entsprechender Verhaltensänderung vergesellschaftet sind. Der Nachweis einer solchen klinischen Vermutung ist im Einzelfall mit implantierten Elektroden gelungen [5].

Prodrome, Symptome und Charakteristika der Patientinnen

Die prodromalen Symptome entsprechen jenen der Enzephalitiden, sind unspezifischer (Kopfschmerzen, Unruhe) oder neuropsychiatrischer Art (Amnesie, Psychose) oder gehen schon mit partiellen, komplex-partiellen oder generalisierten tonisch-klonischen Anfällen einher.

In unserer eigenen, retrospektiven Studie von 13 Patienten dauerte diese prodromale Phase bei der Hälfte der Patienten weniger als eine Woche, bei der anderen Hälfte zwischen 1 Woche und 11 Monaten (mean: 3,3 Monate, median: 1 Monat) [6]. Die Dauer des SE war sehr variabel und lag bei der Mehrzahl der Patienten (9/13) zwischen 1 und 4 Monaten. Die häufigste Form des SE war der generalisierte tonisch-klonische oder nur klonische Anfall, gefolgt von komplex-partiellen Anfällen und vom nicht-konvulsiven SE (NCSE). Fast alle Patienten mussten intensivmedizinisch betreut beziehungsweise intubiert und mechanisch beatmet werden.

Ursprünglich wurde der iSE vor allem bei jungen Frauen (Teratom und anti-NMDAR-AK) und bei Patienten mit kleinzelligem Lungentumor (anti-Hu-AK) diagnostiziert [7]. In den vergangenen Jahren werden aber immer öfter auch Fälle von Kindern [8] und älteren Patienten publiziert [9]. Da sich bei vielen dieser Patienten kein Tumor feststellen lässt, wird ein genuiner, autoimmuner Prozess vermutet. Die Ausweitung der Alterspanne der Patienten, wahrscheinlich in der Mehrzahl Frauen, lässt sich möglicherweise durch eine bessere Kenntnis und leichtere Verfügbarkeit der Tests erklären.

Beschriebene Antikörper

Zurzeit ist es möglich, mehr als zehn verschiedene Antikörper (AK) zu identifizieren, die in der Konstellation des iSE diagnostiziert werden können. Eine gute Übersicht der bisher bekannten AK, deren Epitope und damit assoziierten Syndrome findet sich in der am letzten internationalen Kolloquium zum Status Epilepticus (The 4th London-Innsbruck Colloquium on Status Epilepticus and Acute Seizures, Salzburg, April 2013) von Rebecca Davis und Josep Dalmau präsentierten Arbeit [10]. Es handelt sich dabei um Antikörper, die entweder autoimmuner oder paraneoplastischer Herkunft sind und die Antigene auf der Zellmembran, den Synapsen der Neuronen oder intrazellulär erkennen. Der pathogene Effekt der Oberflächenantikörper durch die Veränderung der synaptischen Aktivität der Neuronen ist nachvollzierbar, kommt aber bei intrazellulären Antigenen weniger in Betracht. Der Beweis, dass die Antikörper exzitatorisch oder inhibitorisch das Zellmembranpotenzial verändern, ist immer noch nicht erbracht. Zudem wird oft beobachtet, dass Patienten auch nach vollständiger Genesung antikörper-positiv bleiben. Die direkte Pathogenizität der Antikörper bleibt also zu beweisen, deren Assoziation mit den beschriebenen Syndromen steht allerdings ausser Frage. Inwieweit jedoch die engmaschige Titerkontrolle sinnvoll ist, wird noch diskutiert. Bei anti-GAD scheint es eine Korrelation zu geben, für andere AK wird dies noch untersucht, bzw. bräuchte es prospektive Studien.

Elektroenzephalogramm (EEG) und Bildgebung

Für die Diagnose des iSE ist der Nachweis von ETP im EEG unerlässlich und obligatorisch für den NCSE. Die Interpretation von rhythmischen oder periodischen Verlangsamungen ist nicht vereinheitlicht und kann zu unterschiedlichen Diagnosen führen (Enzephalitis versus iSE) und spiegelt die Schwierigkeiten der oben diskutierten fliessenden Übergänge wieder.

Interessanterweise ist die Bildgebung initial oft normal, ohne die typische MRI- Hyperintensität im Mesiotemporallappen wie zum Beispiel bei der anti-VGKC-Enzephalitis, und bleibt oft normal trotz Fortbestehen des iSE [6]. Diese Beobachtung korreliert gut mit der ausgezeichneten Prognose gewisser Patienten, es gibt aber keine Studien, die dies belegen. Das MRI kann kortikale, temporale oder hippokampale Hyperintensitäten oder gelegentlich nur eine diffuse Atrophie zeigen.

Funktionelle Bildgebungen wie PET-CT oder SPECT im iSE sind zurzeit nur in sporadischen Fallbeschreibungen zu finden und liefern widersprüchliche Resultate.

Therapeutische Ansätze und Prognosen

Für die Behandlung des konvulsiven SE gibt es mittlerweile gut etablierte Richtlinien, die auf einem Dreistufenschema aufbauen [11], wobei in der ersten Stufe so früh als möglich Benzodiazepine bukkal, rektal oder intravenös verabreicht werden, und, falls der Anfall nicht unterbrochen werden kann, in der zweiten Stufe schnellst möglich ein spezifisches intravenöses Antiepileptikum hochdosiert wird, und in der dritten Stufe, bei fortbestehendem SE, eine Vollnarkose mit Burst-Suppression im EEG angestrebt wird. Auch wenn diese Richtlinien allgemein akzeptiert sind, bestehen ab der zweiten Stufe keine randomisierten, kontrollierten Studien, und die meisten Medikamente werden Off-Label eingesetzt [12]. (Für die zweite Stufe ist zur Zeit eine kontrollierte, randomisierte Studie im Gange [13].) Richtlinien für den nicht-konvulsiven Status sind weniger etabliert, und die meisten Zentren haben ihre eigenen Guidelines. Allgemein gilt zu beachten, dass trotz intensiver antiepileptischer Therapie, der iSE in einen refraktären oder superrefraktären Status Epilepticus (RSE oder SRSE) übergehen kann. Über Anzahl und Frequenz dieses Übergangs bestehen keine genauen Zahlen.

Der immunogene Hintergrund kann oft erst Tage nach dem Auftreten des SE aufgedeckt werden, bedarf des Ausschlusses infektiöser Ursachen, der Suche nach einem unterliegenden Tumorleiden und der Identifizierung des allfälligen Antikörpers. Dies erklärt, warum die immunmodulierende Therapie oft erst Wochen nach dem Auftreten des iSE zum Einsatz kommt. Wenn man davon ausgeht, dass der immunologische Prozess schon Wochen bis Monate vor dem Auftreten des SE eingesetzt hat, wird die zeitliche Verzögerung zwischen Krankheitsbeginn und Therapie noch deutlicher. Es ist also nicht überraschend, dass die immunologische Behandlung oft keine sofortige klinische Verbesserung bringt, was noch nichts über ihre eventuelle Langzeitwirksamkeit aussagt. Auch hier bestehen keine verlässlichen Studien. Dringend nötig wären Studien mit der Fragestellung, ob viel früher eingesetzte immunomodulatorische Therapien die Krankheitsdauer verkürzen beziehungsweise den Übergang in einen SRSE verhindert können.

In Anlehnung an andere immunologische Erkrankungen des ZNS kommen im iSE wie bei den autoimmunen Enzephalitiden in erster Linie hochdosierte Steroide, intravenöse Immunoglobuline oder Plasmapheresen zum Einsatz, und in zweiter Linie Rituximab und Cyclophosphamid. In einer Kohortenstudie von mehr als 500 Patienten mit anti-NMDAR Antikörper-Enzephalitis zeigten die Patienten, die länger und intensiver behandelt wurden, eine signifikant höhere Remissionsrate [14]. Ob dies an der spezifischen immunmodulierenden Therapie oder an der längerdauernden Intensivtherapie liegt, kann die Studie nicht beantworten.

Falls ein Tumorleiden entdeckt und als pathogen

für den iSE erachtet wird, ist dessen Behandlung ausschlaggebend für die Prognose. Bei „gutartigen“ Tumoren wie Ovarialteratomen mit extrazellulären AK (anti-NMDAR) ist die Prognose gut, bei kleinzelligem Lungenkarzinom und intrazellulären AK (anti-Hu) dem onkologischen Kontext entsprechend schlecht. Aber auch hier ist mit der Interpretation der verfügbaren Daten Vorsicht geboten: in unserer oben erwähnten Studie [6] beschreiben wir 2 junge Patientinnen mit Anti-NMDA-Rezeptor-Enzephalitis und SE (bei der einen intermittierend über mehrere Wochen, bei der anderen über 2 Monate), bei denen das Ovarialteratom erst 1 beziehungsweise 2 Jahre nach der vollständigen Remission entdeckt wurde.

Diese Beobachtungen legen die Überlegung nahe, dass es sich beim iSE in gewissen Fällen um einen selbstlimitierenden immunologischen Prozess handeln könnte, der schlecht auf alle bekannten antiepileptischen und immunmodulierenden Therapien anspricht, aber dennoch in vielen Fällen eine gute Prognose hat, sofern die intensivmedizinische Betreuung aufrechterhalten wird. Unserer Erfahrung gemäss und den Diskussionen, die wir mit Kollegen aus dem In- und Ausland hatten, stellt die Tatsache, dass es sich oft um eine chronische Krankheit (Dauer des iSE oft Wochen bis Monate) handelt, eine neue, ungewohnte Herausforderung an die Mitarbeiter der Intensivstation dar. Für die betreuenden Neurologen ist es oft schwierig, nach wochenlangem Koma und SE die Intensivmediziner davon zu überzeugen, dass eine Weiterbehandlung sinnvoll und mit einer potenziell guten Prognose verbunden ist.

Vergleichbar wäre diese Konstellation mit einem Patienten, der unter einer aggressiven und therapierefraktären Form eines Guillain-Barré-Syndroms leidet, über Monate beatmet werden muss und, falls er dies überlebt, dennoch eine gute Prognose hat.

Was den iSE betrifft, scheinen Geduld und Beharrlichkeit – solange noch so viele Fragen offen stehen – die besten Ratgeber in der Behandlung dieser schwierigen Patienten.

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1 Crepeau AZ et al. Levetiracetam: a comprehensive review, Expert Rev Neurother, 2010 Feb. 10(2), 159–171

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Sari ist eine begabte Literaturstudentin, die äusserlich beherrscht und selbstbewusst wirkt. Ihr Leben ist jedoch durch eine gewisse Zurückgezogenheit geprägt. Die Kolleginnen beneiden sie um ihre Intelligenz und Schönheit, die männlichen Komilitonen bewundern sie aus der Ferne aus denselben Gründen. Aber in Saris Innerem lauert eine Bestie, die sie vom Rest der Welt isoliert: die junge Frau hat Epilepsie, eine gefürchtete und geheimnisvolle Krankheit, und die Angst vor Anfällen macht sie vorsichtig. Sie achtet auf eine gewisse Distanz zu anderen Menschen. Als Sari dem älteren Literaturdozenten Mikko Groman begegnet, erkennt sie in ihm ein ähnliches Element von Reserviertheit. Mikko, der sich in seiner ganz eigenen, komplizierten Gedankenwelt bewegt, fühlt sich nur in der Dichtkunst des 19. Jahrhunderts so richtig zuhause. In der leistungsorientierten modernen Welt der Computer und Iphones ist er ein Sonderling. In Mikko findet Sari einen Seelenverwandten, doch in den Augen der anderen scheinen die beiden überhaupt nicht zueinander zu passen.

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Bewerbungen sind **bis zum 31.12.2015** an die **Geschäftsstelle der Epilepsie-Liga** (Seefeldstrasse 84, Postfach 1084, 8034 Zürich) einzureichen und müssen beinhalten: vier Exemplare der abgeschlossenen und beim Dekanat eingereichten Dissertation, vier Exemplare einer Stellungnahme des Doktorvaters (dabei kann es sich auch um das entsprechende Gutachten für die Dissertation handeln).

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Les dossiers de candidature doivent parvenir au Secrétariat de la Ligue contre l'Epilepsie (Seefeldstrasse 84, case postale 1084, 8034 Zurich) jusqu'au

31.12.2015

et comporter les pièces suivantes :

- quatre exemplaires de la dissertation achevée et remise au décanat,
- quatre exemplaires d'une prise de position du directeur de thèse (il peut par exemple s'agir de l'expertise concernant la dissertation).

A noter s.v.p.

La prochaine assemblée générale aura lieu à Zurich (Kongresshaus) le 13 juin 2014 de 13h30 à 14h30.

Abschied von Harry Meinardi (1932 – 2013)

Ende 2013 ist das Korrespondierende Mitglied der Epilepsie-Liga, Professor Harry Meinardi, unerwartet verstorben. Die Epilepsie-Gemeinde trauert um den ehemaligen Präsidenten der International League Against Epilepsy (ILAE) und des International Bureau for Epilepsy (IBE). Hier ein Nachruf von Ted Reynolds, publiziert im Epigraph Newsletter im Winter 2014.

« I first met Harry in June 1968 at the European Epilepsy Conference („European Institute") organised by IBE in Dunblane, Scotland. As Director of Research at a major Dutch Epilepsy Institution Harry's friendly interest in my first research efforts were much appreciated by me at the time. From slightly different backgrounds we have since then been in regular contact as colleagues, collaborators and friends through our common interest in the science, treatment, care, politics and history of epilepsy.

Throughout the 1970s we both participated in the biennial « Workshops on the Determination of Antiepileptic Drugs in Body Fluids », the so-called WODADIBOF Meetings. In the late 1960s and early 1970s blood level monitoring of antiepileptic drugs was a new scientific frontier in epilepsy and Harry initiated the first meeting in Heemstede in 1972. During the 1980s we met at a series of British/Danish/Dutch ILAE Chapter meetings, culminating in the Northern European Symposium, i.e. including other Scandinavian countries, in 1989. From 1989 to 1993 Harry was President of ILAE and I had the pleasure of supporting him on the Executive as a Vice President. When I succeeded him as President (1993-1997) Harry was likewise a very supportive Past President.

Throughout the last 45 years there have been innumerable friendly encounters at international, regional and national Conferences or Symposia (e.g. neurotransmitters, memory functions etc) throughout the world. I particularly remember in 1991 Harry and I were both invited to lecture in Messina in Sicily and our reward was a delightful all day boat trip to the Aolian Islands, escorted by Raoul Di Perri and Franco Pisani. I also recall the occasional pleasant visit to Heemstede and to Harry's home in The Hague.

I last met Harry, appropriately enough, at the Centenary Congress of ILAE in Budapest in 2009, but since then we have continued to keep in touch and collaborate on a series of articles on the history of IBE and ILAE in International Epilepsy News.

The Netherlands has been at the forefront of the Epilepsy Movement before and since the foundation of ILAE in Budapest in 1909, in which Harry's country played a leading role. As Director of one of the most famous Epilepsy Centres in the world Harry was the epitome of that tradition following in the footsteps of Louis Muskens, Bernard Christian Ledebor, Albert Lorentz de Haas, Otto Magnus and Joob Loeber. Harry, however, was unique among them and indeed all other epileptologists in serving as President of both the Bureau (1977-1981) and the League (1989-1993). This of course reflected his commitment to every aspect of patient care and academic epileptology, from the neurochemical and neuropharmacological to the medical, social and political. This also culminated in his apointment as perhaps the first Professor of Epileptology in the world.

Harry's whole career was committed to people with epilepsy locally, nationally and internationally. This he carried out with great dedication, skill and diplomacy. He had a friendly and engaging style, facilitated by an almost British sense of humour, which endeared him to his professional colleagues. He was not driven by any philosophical or religious inclinations, but by practical, humanitarian and diplomatic considerations, with enormous attention to detail. The epilepsy movement has lost a great champion, reflected in his many achievements. I will personally miss our regular, friendly, humorous but ultimately serious and constructive interactions over nearly five decades. »

2014

8.-11.5.2014 | Berlin, Deutschland
8th World Congress 2014 – Controversies in Neurology
Information: comtecMED, Medical Congresses,
53 Rothschild Boulevard, PO Box 68, Tel Aviv,
6100001, Israel,
Tel. 00972 / 3 / 5666166,
Fax 00972 / 3 / 5666177,
e-mail: Info@comtecmed.com,
www.comtecmed.com

14.-17.5.2014 | Bonn, Deutschland
52. Jahrestagung der Deutschen Gesellschaft für Epileptologie
Information: Conventus Congressmanagement & Marketing GmbH, Juliane Börner,
Carl-Pulfrich-Strasse 1, D 07745 Jena, Deutschland,
Tel. 0049 / 3641 / 3116347,
Fax 0049 / 3641 / 3116243,
e-mail: epilepsie@conventus.de
www.conventus.de

22.5.2014 | Luzern, 17 Uhr
Fachveranstaltung der Epilepsie-Liga
Information: Epilepsie-Liga,
Seefeldstrasse 84, Postfach 1084, 8034 Zürich,
Tel. 0041 / 43 / 4886777,
Fax 0041 / 43 / 4886778,
e-mail: info@epi.ch
www.epi.ch

22.5.2014 | Luzern, 19.30 Uhr
Publikumsveranstaltung der Epilepsie-Liga
Information: Epilepsie-Liga, Seefeldstrasse 84,
Postfach 1084, 8034 Zürich,
Tel. 0041 / 43 / 4886777,
Fax 0041 / 43 / 4886778,
e-mail: info@epi.ch
www.epi.ch

22.-24.5.2014 | Cape Town, Südafrika
2nd African Epilepsy Congress (AEC)
Information: ILAE/IBE-Congress Secretariat,
7 Priory Hall, Stillorgan Road, Blackrock, Co. Dublin,
Ireland,
Tel. 00353 / 1 / 2056720,
Fax 00353 / 1 / 2056156,
e-mail: capetown@epilepsycongress.org

28.-30.5.2014 | Marburg, Deutschland
7. International Epilepsy Colloquium „Diagnostic and therapeutic use of intracranial electrodes“ sowie Satellitensymposium „Status epilepticus“
Information: Congrex Deutschland GmbH,
Hauptstr. 18, D 79576 Weil am Rhein, Deutschland,
Tel. 0049 / 7621 / 9833-0,
Fax 0049 / 7621 / 78714,
e-mail: weil@congrex.com

31.5.-3.6.2014 | Istanbul, Türkei
Joint Congress of European Neurology (SNG/SSN) Sponsorpool 2014 / Joint Meeting European Neurological Society (ENS) and European Federation of Neurological Societies (EFNS)
Congrex Switzerland, Peter-Merian-Strasse 80,
P.O. Box, 4002 Basel,
Tel. 0041 / 61 / 6867777,
Fax 0041 / 61 / 6867788,
e-mail: secretariat.istanbul2014@congrex-switzerland.com
www.congrex-switzerland.com

5.-7.6.2014 | San Francisco, USA
Epilepsy Foundation‘s 2014 Pipeline Conference to Showcase Innovation and Advancements in the Treatment of Seizures
Information: Epilepsy Foundation, 8301 Professional Place, Landover, MD 20785, U.S.A.
www.epilepsy.com

12.-13.6.2014 | Zürich, Kongresshaus
Joint Annual Meeting 2014 SSNS, SSCN, SSNP, IG-NOPPS and SFND/ASDN
Information: www.imk.ch/ssn2014

29.6.-3.7.2014 | Stockholm Schweden
11th European Congress on Epileptology
Information: ILAE/IBE-Congress Secretariat,
7 Priory Hall, Stillorgan Road, Blackrock, Co. Dublin,
Ireland,
Tel. 00353 / 1 / 2056720,
Fax 00353 / 1 / 2056156,
e-mail: Stockholm@epilepsycongress.org
www.epilepsystockholm2014.org

3.-8.8.2014 | Trakai, Litauen
8th Baltic Sea Summer School on Epilepsy
Information: petra.novotny@wolfstiftung.org,
www.epilepsie-stiftung-wolf.de

7.-10.8.2014 | Singapur
7th Asian & Oceanian Epilepsy Congress
Information: ILAE/IBE-Congress Secretariat,
7 Priory Hall, Stillorgan Road, Blackrock,
Co. Dublin, Ireland,
Tel. 00353 / 1 / 2056720,
Fax 00353 / 1 / 2056156,
e-mail: singapore@epilepsycongress.org,
www.epilepsysingapore2014.org

04.-07.09.2014 | Basel
The World Congress on NeuroTherapeutics: Dilemmas, Debates & Discussions (DDDN)
Information: NeuroTherapeutics Secretariat,
CongressMed, 20 Lincoln St., Floor 13, Tel Aviv 67134, Israel,
Tel. 00972 / 73 / 7066950,
e-mail: dddn@congressmed.com,
www.congressmed.com/neurology/

17.-20.9.2014 | Buenos Aires, Argentinien
8th Latin American Congress on Epilepsy
Information: www.epilepsycongress.org

18.-20.09.2014 | Oldenburg, Deutschland
29. Jahrestagung der Gesellschaft für Neuropsychologie
Information: Valerie Stähler, Kongress- und Messe Büro Lentzsch GmbH Büro: Gartenstr. 29,
D 61352 Bad Homburg, Deutschland
Tel. 0049 / 6172 / 67960,
Fax 0049 / 6172 / 679626,
e-mail: valerie.staehler@kmb-lentzsch.de
www.kmb-lentzsch.de

21.-24.09.2014 | Gargnano, Italien
26. Praxisseminar über Epilepsie und EEG
Information: Stiftung Michael Alsstrasse 12,
53227 Bonn, Deutschland,
unterstützt von Desitin,
Tel. 0049 / 228 / 94554540,
Fax 0049 / 228 / 94554542,
e-mail: post@stiftung-michael.de,
www.stiftungmichael.de

25.9.2014 | Lugano, 14 Uhr
Fachveranstaltung der Epilepsie-Liga
Information: Epilepsie-Liga,
Seefeldstrasse 84, Postfach 1084, 8034 Zürich,
Tel. 0041 / 43 / 4886777,
Fax 0041 / 43 / 4886778,
e-mail: info@epi.ch
www.epi.ch

25.9.2014 | Lugano, 19.30 Uhr
Publikumsveranstaltung der Epilepsie-Liga
Information: Epilepsie-Liga,
Seefeldstrasse 84, Postfach 1084, 8034 Zürich,
Tel. 0041 / 43 / 4886777,
Fax 0041 / 43 / 4886778,
e-mail: info@epi.ch
www.epi.ch

29.10.-31.10.2014 | Interlaken
SNG-Tagung - Gemeinsame Jahrestagung mit der Schweizerischen Gesellschaft für Intensivmedizin (SGI), Schweizerischen Gesellschaft für Neurologie (SNG), Schweizerischen Gesellschaft für Neuroradiologie (SGNR), Schweizerischen Hirnschlaggesellschaft (SHG), Schweizerischen Gesellschaft für Notfall- und Rettungsmedizin (SGNOR), Gäste: Schweizerische Gesellschaft für Verhaltensneurologie (SGVN), Schweizerische Liga gegen Epilepsie SLgE
Information: http://www.imk.ch/sgi2014

17.-18.11.2014 | Zürich
Aufbaukurs Epilepsie
Information: Jörg Wehr, Bildung und Öffentlichkeitsarbeit, Schweiz. Epilepsie-Stiftung,
EPI WohnWerk, Bleulerstr. 60, CH 8008 Zürich
Tel. 0041 / 44 / 3876480,
Fax 0041 / 44 / 3876138,
e-mail: joerg.wehr@swissepi.ch
http://www.epi.ch/_admin/02_cms/
www.epi-wohnwerk.ch

5.-9.12.2014 | Seattle, Washington, USA
68th Annual Meeting of the American Epilepsy Society
Information: American Epilepsy Society, 342 North Main Street, West Hartford, CT 06117-2507 USA,
Tel. 001 / 860 / 5867505,
Fax 001 / 860 / 5867550,
e-mail: info@aesnet.org, www.aesnet.org

Impressum

Herausgeber | Administration | Schlussredaktion
Schweizerische Liga gegen Epilepsie
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Konzeption | Gestaltung | Reinzeichnung
screenblue Büro für Design | Birgit Depping
Gazellenkamp 99, D-22529 Hamburg
bd@screenblue.de, www.screenblue.de

Belichtung | Druck
J.C.C. Bruns Betriebs GmbH
D-32423 Minden, www.jccbruns.de

Auflage
1.200 Exemplare

Versand
Eingliederungs- und Dauerwerkstätte
des Schweiz. Epilepsie-Zentrums
Bleulerstrasse 72, 8008 Zürich