Autoimmune Epilepsies

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Abstract In patients with immune-associated disorders of the gray central nervous system matter (including recurrent seizures), antibodies against intracellular antigens have been discovered since the 1980s/1990s. In recent years, new antibodies against surface antigens have also been discovered. In two respects, these antibodies are even more interesting than the ones to intracellular antigens as, first, they promise a better response to immunotherapy; and, second, these antibodies contribute greatly to the understanding of the disease mechanisms. Whereas in encephalitides with antibodies against intracellular antigens, a cytotoxic T-cell-mediated response seems to be responsible for neuronal cell loss, in encephalitides with autoantibodies against surface antigens these antibodies are probably the relevant pathogenic agents in the associated disease conditions. On the one hand, antibodies to the NR1 subunit of N-methyl-D-aspartate receptors have been suggested to cause internalization and loss of these receptors without any cell destruction. This mechanism can explain the reversible functional effects caused by these antibodies. On the other hand, antibody- and complement-mediated destructive, and the irreversible effects of antibodies against the voltage-gated potassium channel antigens have been noted. These emerging findings make it plausible that immunological therapies, preferably early after characterization of the antibodies, offer opportunities to restore the health of affected patients.

Keywords Antibody-associated · limbic encephalitis · epilepsy · seizures

Introduction

The concept of antibody-associated central nervous system (CNS) disorders appeared for the first time in the 1960s. At this time, Lord Brain reported on a patient with an encephalopathy who was previously diagnosed with Hashimoto's thyroiditis in the presence of anti-thyroid antibodies. Eventually, after recovery of the patient, Brain et al. [1] suggested that autoimmune mechanisms might be involved in such unexplained encephalopathies. Subsequently, further reports on the concept of "Hashimoto's encephalopathy" appeared. Influential work from Bern, Switzerland [2], even distinguished different clinical types of "Hashimoto's encephalopathy". Most recently, it has been suggested that at least a part of these cases have antibodies to presently defined neuronal surface antigens, so that the thyroid antibodies must be viewed as bystanders [3]. In the 1980s, antibodies against glutamic acid decarboxylase (GAD) and against "onconeural" antigens were detected [4]. The latter antibodies are directed to (extracerebral) tumors that cross-react to intranuclear antigens in neurons. Such antibodies occur almost exclusively in patients with paraneoplastic CNS disorders [5, 6], which have been reviewed in several articles [7–9]. The discovery of antibodies directed against neuronal surface proteins rather than intracellular or intranuclear antigens was conceived as a breakthrough in neurology [10, 11]. A reason for this is that, in contrast to cases with GAD antibodies and antibodies to onconeural antigens, patients with antibodies against surface antigens can be successfully treated with immunotherapies.

The most frequently found antibodies are those to the N-methyl-D-aspartate (NMDA) receptor and to leucine-rich,

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glioma-inactivated 1 (LGII), a protein associated with the voltage-gated potassium channel (VGKC) complex. NMDA receptor antibodies usually are found in young women with often severe, but reversible, encephalopathies [12]. LGII antibodies, however, are often detected in elderly people with limbic encephalitis presenting with temporal lobe seizures and disturbance of recent memory [13] or faciobrachial dystonic seizures [14, 15]. Approximately three-quarters of CNS disorders with antibodies to surface antigens present with epileptic seizures [16]. Clinical features in antibody-associated “autoimmune epilepsies” may not always be absolutely typical for the described clinical syndromes, but still be responsive to immunological therapies [17].

Studies on the pathophysiology of the associated brain disorders show that the individual antibodies against surface antigens exert different pathophysiological effects on the CNS. We present an overview of the existing knowledge on this. In summarizing the existing data, we tentatively suggest a dichotomy between mechanisms causing functional and thereby potentially reversible disruption of neuronal activity without death of nerve cells and mechanisms leading to both functional and structural damage. Consequently, antibody removal in the first case will permit restoration of the previous function while in the latter, owing to the structural damage, improvement with remaining deficits will occur. The current data come from studies that investigated antibodies and their potential effects on neurons. First, there are *in vitro* studies and studies in experimental animals [18–22]. Second, there are studies focusing on the “the other side”, that is the target organ. Such studies on the brains of patients with antibody-associated diseases have used positron emission tomography [23], resting state functional magnetic resonance imaging (MRI) [24], or neuropsychology tests [25, 26] for functional studies, or MRI and histopathology for structural investigations [24, 27–32]. As far as possible, this review will consider the specific issue of epileptogenesis in the context of these encephalitides. After a review of the data on antibodies to intracellular antigens, we will focus on the surface antigen-directed antibodies, that is anti-VGKC complex (mainly anti-LGII) and anti-NMDA receptor (NMDAR). These two are the most frequently observed and most intensely studied antibodies to date.

Studies with Antibodies Against Intracellular Antigens

This group comprises the onconeural antibodies—the most frequently observed and studied ones are directed to Hu, Yo, and GAD [33]. Encephalitides with onconeural antibodies often affect the limbic system (limbic encephalitis) and lead to epileptic seizures [34]; other manifestation sites are the peripheral nervous system (in cases with Hu antibodies) or the cerebellum (in cases with Hu or Yo antibodies) [35, 36]. The rare longitudinal studies of these conditions suggest

destructive courses evident by progressive limbic, but also neocortical atrophy on serial MRIs [31]. *In vitro* studies on the pathogenic effect of intra-nuclear antibodies have given contradictory results. On the one hand, studies with Hu (and other onconeural antibodies) have shown that these can be taken up by neurons, but do not seem to damage these cells [37, 38]. Other studies with Hu antibodies, on the other hand, have suggested that these antibodies can, indeed, induce cell death in neuronal cultures [39]. In various transfer approaches repeated attempts have been made to induce disease symptoms or pathological changes by transfer of patient sera with Hu or Yo antibodies into experimental animals. With some exceptions [40], these studies generally did not show antibody-induced cell death [41–44]. Probably one of the reasons for this failure to induce cell death after transfer or injection of antibodies into the brain is that, even if they reach the targeted neurons, the antibodies cannot enter the cytoplasm of these intact cells.

How is then neurodegeneration in the brains of patients with these types of encephalitis induced? Detailed immunopathological studies of biopsies and autopsies of such brains provide a good explanation for this. In specimens from patients with onconeural antibodies, an intense T-cell-mediated inflammation with clear evidence of a cytotoxic T-cell response via the perforin–granzyme B pathway has been found [27, 45].

Patients with GAD antibodies and limbic encephalitis with seizures usually have a chronic course. In some patients, there is also evidence for progressive loss of brain tissue, mainly in the medial temporal lobe [46]. The findings in brain tissue from such GAD antibody-positive patients are less clear, but also consistent with a cytotoxic mechanism [27]. A nerve cell destroying T-cell effect is certainly compatible with the progressive focal or generalized brain atrophy in patients with GAD antibodies [31, 46]. In analogy to other CNS disorders with neuronal degeneration, that is mediotemporal epilepsy with hippocampal sclerosis, such neuronal loss could explain both the patients’ epilepsies and their memory problems [47]. Another question is which antigens are recognized by the cytotoxic T-cells? One of the first diseases in which this was investigated was paraneoplastic cerebellar degeneration. Investigations by Darnell et al. and Tanaka et al. [48–50] in patients with anti-Yo antibodies showed that the blood of these patients also contains cytotoxic T-cells specific for the Yo antigen. Similarly, patients with anti-Hu antibodies also have cytotoxic T-cells that recognize Hu antigens [51]. These results suggest that in patients with paraneoplastic encephalitis the immune system creates both a cytotoxic T-cell response and a humoral response against the same neoplastic antigens. Most likely, these antigen-specific activated T-cells cross the blood–brain barrier (BBB) and attack the neurons that express these antigens in a major histocompatibility complex class I restricted

manner. Such mechanisms have been shown in various animal models [52–55].

Antibodies Against Antigens That Are Part of the VGKC complex

VGKC complex antibody encephalitis can be found in paraneoplastic patients [56, 57], but are not usually associated with a tumor [58, 59]. It has recently been shown that these antibodies are directed to proteins that are associated with the VGKC complex, rather than with the VGKC itself. Until now, three different target proteins have been recognised: contactin-associated protein-like 2 [60, 61], LGI1 [13, 60], and—almost never functioning as sole antigen—the protein Contactin-2 [13, 60, 61]. In most cases, the antibodies are directed against LGI1 [13, 60]. Clinically, these patients present with memory loss, confusion, behavioral changes, and, in more than two-thirds of cases, with seizures [58, 62]. In addition, some cases with contactin-associated protein-like 2 antibodies present with cerebellar ataxia [63, 64]. Other manifestation sites are the neuromuscular junction in acquired neuromyotonia or Isaacs syndrome, or a combination of both CNS and peripheral nervous system manifestations, called Morvan syndrome [60, 61]. Within the group of patients with LGI1 antibodies a subgroup has been recognized, which, shortly before the cognitive changes, present a rather specific prodromal phase with faciobrachial dystonic seizures (FBDS) [14, 15]. Interestingly, this unique seizure type was recognized only as a result of a close collaboration between epileptologists and neuroimmunologists. In 2008, a UK group published three cases with this unusual semiology; all harbored VGKC complex antibodies in their sera and recovered well upon immunological therapy (corticosteroids and intravenous immunoglobulins) [65]. Once recognized, the group and referring physicians who had become aware of the 2008 report spotted another 29 patients with this seizure type. Again, all these patients had VGKC complex antibodies; in 23 of them the antibodies were directed to LGI1 [14]. Thereafter, another 10 such cases were identified prospectively and published recently [15].

There is some controversy over whether FBDS are truly epileptic seizures or a kind of movement disorder. There are arguments in favor of both. Recently, it has been suggested that the traditional border zones between epilepsy and movement disorders with (nearly) exclusive cortical *versus* basal ganglia pathogenesis are not appropriate for FBDS. Imaging studies suggest that a simultaneous involvement of frontal cortex and basal ganglia contribute to this type of event [66].

Evidence that autoantibodies against neural surface antigens can, indeed, cause CNS disease is still scarce. In earlier studies, the transfer of anti-glutamate receptor 1 antibodies into the brains of mice elicited the symptoms of human glutamate receptor 1 antibody-associated disease, that is ataxia

[67, 68]. More recently, the transfer of sera containing antibodies against aquaporin-4 from patients with neuromyelitis optica induced cell death in the CNS in different experimental models [69–71]. Antibodies against the proteins associated with the VGKC complex have only recently been tested for pathogenicity. Potentially reversible, non-destructive effects have been documented in a single case study for LGI1 antibodies. Lalic et al. [20] incubated rat hippocampi with the IgG of a patient with limbic encephalitis, with LGI1 antibodies and with control IgG. They showed a binding of LGI1 antibody-positive material to hippocampal neuropil. In subsequent electrophysiological studies, they demonstrated an increase of after-discharges in the stratum lucidum of the CA3 sector upon extracellular stimulation. At the single cell level, the presence of anti-LGI1 antibodies led to an increased rate of spontaneous depolarizations. This effect could be mimicked by the VGKC blocker dendrotoxin. Lalic et al. [20] concluded that in patients with high LGI1–IgG antibody titers the antibodies reduce the VGKC synaptic function and thereby increase the cellular excitability. With this they provided a preliminary explanation for the high propensity of epileptic seizures in patients with LGI1 antibodies.

Although these experiments show a pathological effect of LGI1 antibodies in rat brain, these experiments do not fully explain the pathology seen in human brain. In patients with VGKC complex encephalitis (usually with antibodies to LGI1) hippocampal atrophy may develop [27, 72]. Neuropathological studies have shown that brains of patients with VGKC complex antibodies have lymphocytic infiltration [28, 30], but reveal no evidence of T-cell cytotoxicity [27]. Nevertheless, as predicted by the imaging courses, stainings for neurons revealed the presence of degenerating cells. Further investigations demonstrated deposition of immunoglobulin and C9neo on neurons. C9neo activation is the final step of the classical complement cascade, leading to lytic cell death [27] as the probable cause of neuronal degeneration in this disease. This massive neuronal degeneration also may explain why some patients respond poorly or are left with clinical deficits after immunotherapy [25]. The experiments by Lalic et al. [20], in which they induced epileptiform activity by anti-LGI1 antibodies, most likely reflect only some of the pathogenic properties of sera/cerebrospinal fluid (CSF) containing VGKC complex/LGI1 antibodies. This is probably owing to their *in vitro* model, which lacks a complete immunological system needed to induce the pathological changes seen in human brain.

Recently, a new natural model of LGI1 encephalitis has been presented. Publications show that domestic cats can suffer from epilepsy with orofacial seizures that show some similarities to the dystonic faciobrachial seizures in patients with LGI1 antibodies [14]. Interestingly, cats with such seizures can also be found to present with LGI1 antibodies [73, 74]. Neuropathological investigation of these cats shows a severe hippocampal degeneration in the presence of complement C9neo deposition

on the surface of neurons. Massive hippocampal degeneration can be detected within the first week of disease duration [75]. Again, these findings are almost identical to the findings in patients with VGKC complex antibody encephalitis [27], and suggest that in both humans and cats an unknown trigger can induce this complement-mediated progressive hippocampal atrophy. In summary, it is plausible to assume that an (LGI1?) antibody-induced complement activation could be the basis of the abovementioned progressive hippocampal atrophy.

Antibodies Against NMDAR

Anti-NMDAR encephalitis was first described in patients with paraneoplastic encephalitis resulting from ovarian teratomas [76]. Some years later it was shown that the antibodies reacted with the NR1 subunit of the NMDAR [77]. This and other publications also showed that NMDAR encephalitis also could be found in the absence of a tumor [77, 78]. Clinically, patients present with seizures, memory loss, and psychiatric symptoms, such as fear, insomnia, anxiety, mania, and paranoia. Some of these cases rapidly develop movement disorders, oro-lingual-facial dyskinesias, and may become unconscious with autonomic manifestations, such as central hypoventilation [77–79]. In recent years, functional data have become available for NMDAR antibodies. Hughes et al. [18] showed *in vitro* that this antibody cross-links NMDA receptors, thereby causing their internalization into the cell. Earlier, this mechanism was suggested as the key to the pathophysiology of myasthenia gravis with antibodies to the acetylcholine receptor [80]. The internalization of the NMDAR results in a reversible hypofunction without destruction of the nerve cells or synapses [18]. This is a good explanation for the psychotic features often found in anti-NMDAR encephalitis. Another typical feature of the anti-NMDAR encephalitis, episodic memory impairment, can be modeled by suppressing long-term potentiation through antibodies [81]. However, the frequent occurrence of seizures [82], and even status epilepticus [83], is not easily explained by an NMDAR hypofunction, as NMDAR blockers exert an antiepileptic effect and have been considered as treatment option in status epilepticus [84].

Manto et al. [21] provided *in vivo* evidence that the presence of NMDAR antibodies in the CSF was associated with an elevated concentration of glutamate in the extracellular space of the brain. This glutamate increase was positively correlated with the concentration of the antibody. These experiments suggested that CSF with NMDAR antibodies affected the synaptic regulation of glutamate via NMDAR depending on either the NMDAR or the α -amino-3-hydroxy-5-methyl-4-isoxazole propionic acid receptor. The authors did not, however, find evidence to suggest that the glial glutamate transport was affected. A gamma-aminobutyric acid type A receptor blockade resulted in an increase of extracellular glutamate

concentrations after pretreatment with patient CSF containing NMDAR antibodies [21]. These results support a direct change in the glutamatergic signal transmission through NMDAR antibodies. Further evidence for this was provided by Zhang and co-workers. In their *in vitro* experiments, NMDAR antibody-containing CSF suppressed the induction of long-term potentiation in mouse hippocampal slices. Thus, the electrophysiological correlate of “learning” could be interrupted by NMDAR autoantibodies in the hippocampus. This mechanism provides an explanation for the profound anterograde amnesia of patients during the acute phase of illness [81]. Resting state studies using functional MRI point into the same direction; patients with anti-NMDAR encephalitis displayed reduced functional connectivity of the hippocampi with the anterior default mode network. Connectivity of both hippocampi predicted memory performance in patients. [24].

A rather characteristic feature of anti-NMDAR encephalitis is the psychotic manifestations in many of these patients. Further evidence that binding of antibodies to the NMDAR and the internalization of NMDAR can be related to psychosis comes from brain positron emission tomography of patients during the acute phase of the disease. Leyboldt et al. [23] documented a reversal of the normal metabolism of posterior gradient (high metabolism) to anterior (low metabolism), which normalized during clinical recovery. They interpreted the pattern of anterior hypermetabolism and posterior hypometabolism as the result of impaired NMDAR function as similar changes have been observed in psychosis due to the NMDAR antagonist ketamine. It may take up to 2 years and even longer before patients recover fully from anti-NMDAR encephalitis [12, 26]. This cannot, however, be explained by gross brain tissue loss. Neither MRI studies [24] nor histopathology studies have provided evidence for neuronal or other brain tissue loss [27, 32].

Summary and Outlook

The antibodies directed against surface antigens as presented here appear to contribute directly to the disease process in affected patients. However, they do so differently: by receptor internalization, by complement activation, or by some, still to be elucidated, channel interaction. The pathogenesis of these diseases is, however, not yet fully understood. A full understanding would need explanations of several other mechanisms. First, what leads to the formation of these pathogenic antibodies, and what processes do sustain their production? Whereas in paraneoplastic encephalitis a humoral response against tumor antigens is understandable, the formation of anti-neuronal antibodies in non-paraneoplastic cases remains completely unclear. Furthermore, it is striking that, in most cases, only antibodies against one specific antigen are found. Antibody testing for a large panel of different antibodies in most cases is not always performed, which may be a reason

that the presence of multiple autoantibodies is underestimated. However, centers that perform a lot of antibody testing report that only 10 % of the tested cases have more than 1 single antibody [85]. Another interesting point is that the persistence of antibodies over time is different across the antigenic specificities: LGI1 antibodies are often monophasically formed, whereas onconeural antibodies [86] and GAD antibodies [46] persist for long periods, that is they are continuously produced. Another issue is how and why the antibodies reach the brain. Normal brain is shielded by the BBB and blood–CSF barrier. Animal models for multiple sclerosis have shown that antibodies can only reach the brain if they are co-transferred with activated T-lymphocytes, which are thought to open the BBB [87]. Although we know that in antibody-associated encephalitides few or moderate numbers of T-lymphocytes enter the brain, we know hardly anything about their phenotype and if they are involved in opening the BBB. Finally, what role the intrathecally-produced antibodies play in the pathogenesis of antibody-associated encephalitides remains unclear [11]. Immunological and neuropathological studies at early stages of disease, especially in surface antigen-specific cases, could give some answers to these questions. Paradoxically, although beneficial for these patients, the improvement of diagnostic and therapeutic strategies makes it more difficult to collect and study tissues for new cases. This, again, underlines the importance of new and eligible animals models for future studies of these diseases.

Even though many issues still require clarification, for theoretical reasons and supported by clinical experience, it is conceivable that immunological therapies can be very effective in patients with antibodies to surface antigens. It appears most plausible to use therapies that reduce the antibody levels and suppress their formation. One option is the use of traditional immunological approaches—the use of “broad” immunosuppressors, of intravenous immunoglobulins, or of apheresis techniques aimed at reducing antibody levels in the bloodstream—and, indirectly, via the subsequent establishment of a new diffusion equilibrium, the CNS. Whereas a combination of immunoglobulins, cyclophosphamide, and methylprednisolone is of limited effect on conditions with onconeural antibodies, similar immunological polytherapies—partly including apheresis techniques—led to rapid improvements in patients with antibodies to surface antigens, such as the VGKC complex [88, 89]. Based on a retrospective outcome evaluation, Josep Dalmau et al. [79] suggest a scheme of first- and second-line therapy for anti-NMDAR encephalitis (with removal of the tumor if it is a paraneoplastic condition). In their experience, patients who do not respond to first-line therapy within 10 days should be switched to second-line therapy. First-line agents include corticosteroids, intravenous immunoglobulins, and apheresis, given alone or in combination. Second-line agents include rituximab or cyclophosphamide, or both [79]. In a subsequent retrospective analysis of nearly 600 patients, it was shown that first-line

nonresponders with a switch to second-line therapy have better improvement than those who are not given second-line treatment [12]. It also appears plausible to use this general scheme in patients with other antibodies to surface antigens.

With emerging insights into the pathophysiology of the disorders, it is tempting to speculate about an antibody-specific use of the most modern immunotherapeutics with very specific targets. The more T-cell-driven conditions with antibodies to intracellular antigens might benefit from lymphocyte-directed interventions, such as natalizumab. Alemtuzumab (which clears all lymphocytes from the circulation) may act against pathogenic T-cells, but may also help in B-cell-/antibody-mediated disease. Its use in a single case has been reported [90]. Anecdotally, bortezomib, directed against antibody-producing plasma cells, has been used in anti-NMDAR encephalitis, although with inconclusive results [91]. If the hypothesis of a pathogenic complement activation in VGKC complex/LGI1 encephalitis holds true, the use of eculizumab might be attractive. This recombinant humanized monoclonal antibody inhibits the terminal portion of the complement cascade. It has recently been found to produce promising results in another antibody-/complement-mediated neurological disease, neuromyelitis optica [92]. It should be noted, however, that, at present, trial designs for these disorders are lacking. Placebo controls, a classical element in trials of antiepileptic drugs, are conceived as ethically difficult in severely affected patients. The situation may be different in patients with less aggressive courses, for example with a phenotype dominated by epileptic seizures at an “acceptable” frequency—as suggested recently [93], accompanying one of the first open studies with a very promising outcome on the effect of immunotherapy in “autoimmune epilepsy” [17].

Conflict of Interest CG Bien performs serum and CSF antibody analysis for external centers. For these diagnostics his hospital receives fees to cover the costs. CG Bien has received travel expenses from Eisai, UCB, Desitin, and Grifols; lecture fees from Eisai, UCB, GlaxoSmithKline, Desitin, diamed, and Fresenius; and fees for participation in advisory boards of UCB and Eisai. His laboratory research is supported by diamed and Fresenius.

Required Author Forms Disclosure forms provided by the authors are available with the online version of this article.

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