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Review

Antineuronal autoantibodies in neurological disorders

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Abstract

Autoantibodies (abs) related to neurological disease are currently classified into two large groups depending on the site of the respective target antigen: Group I encompasses abs that recognise intracellular antigens (Hu, Yo, Ri, CV2/CRMP5, amphiphysin, Ma2, SOX, ZIC, GAD, adenylate kinase 5, homer 3), whereas group II abs are targeted against neuronal cell membrane antigens (VGKC, AMPA-R, $GABA_B$-R, NMDA-R, Glycine-R, VGCC, metabotropic GluR1). Both abs groups can be further subdivided according to their diagnostic impact for paraneoplastic or non-paraneoplastic neurological disease. The review gives an overview of the common characteristics of each group and provides more detailed information on single abs and the associated clinical syndromes.

Keywords: antineuronal autoantibodies; onconeural antibodies.

Introduction

In the 1980s, a variety of autoantibodies (abs) related to cancer had been identified in patients suffering from paraneoplastic neurological syndromes. These disorders are considered secondary immune mediated effects of cancer (1). The abs involved are thought to result from an immunological response to the tumour tissue. Their clinical relevance had initially been questioned, since the human condition could not be reproduced in animal models, the respective antigens were often of intracellular localisation and selective types of neurons were found involved despite a more widespread antigen expression. During the recent years, additional abs directed against neuronal surface antigens have been identified in patients suffering from paraneoplastic and non-paraneoplastic neurological syndromes (1). This has corroborated the concept of neurological disease mediated by abs against central nervous system (CNS) antigens mediating neurological disease.

Abs related to neurological disease are currently classified into two large groups depending on the site of the respective target antigen: Group I encompasses abs that recognise intracellular antigens, whereas group II abs are targeted against neuronal cell membrane antigens. Both groups can be further subdivided according to their diagnostic impact for paraneoplastic or non-paraneoplastic neurological disease (see Table 1). This review describes the most frequent antineuronal abs with special emphasis on the nature of the underlying tumour, other potential aetiologies, associated clinical symptoms and their response to therapy as well as their immunological and functional aspects.

Group Ia: abs directed against neuronal intracellular antigens: Hu, Yo, Ri, CV2, amphiphysin and Ma2

Classical onconeural abs are directed against target antigens in neuroectodermal tissues and related tumours. They have been designated as ‘onconeural abs’. Group Ia abs always target intracellular antigens (2). Evidence of immunoreactivity with antigens shared by the tumour and neuronal cells constitutes not only the pathophysiological background but also the diagnostic basis for the diagnosis of the paraneoplastic neurological syndrome (2). As a matter of fact, there is currently no experimental evidence that group Ia abs directly contribute to the pathogenesis of the associated paraneoplastic neurological syndromes (2): the active vaccination with their intracellular target antigens or their experimental passive transfer does not reproduce the human condition in animal models. However, there is one exception: the passive transfer of IgG from an individual suffering from stiff person syndrome with amphiphysin abs did elicit transient spasms in a rat model. It has been speculated that this effect could be due to other abs than those against amphiphysin in the patient’s serum (3) or that amphiphysin that is involved in the turnover of synaptic vesicles could be transiently exposed on the cell surface thereby mimicking group II abs (4).

Group Ia abs overwhelmingly belong to IgG subclasses capable of fixing complement. Neuropathologic studies demonstrate perivascular and parenchymatous inflammatory infiltrates that consist of CD8 positive cytotoxic lymphocytes. This supports cytotoxic T cell mechanisms directed against the same antigens that are targeted by the abs. Indeed, Hu- and Yo-specific CD8 cytotoxic lymphocytes have been isolated from the blood of paraneoplastic neurological syndromes patients (5, 6). They are capable of killing target cells in an HLA-restricted manner. In this setting, group Ia abs would constitute the humoral response of a more complex immune reaction. However, group Ia abs are of major diag-

Table 1 Classification of antineuronal autoantibodies.

	Abs (name of antigen)
Group I: abs against neuronal intracellular antigens	
a. Diagnostic markers for paraneoplastic neurological syndromes that predict a certain type of associated tumour	• Hu • Yo • Ri • CV2/CRMP5 • Amphiphysin • Ma2
b. Cancer-specific abs that are not considered pathogenic for the associated paraneoplastic neurological syndromes	• SOX • ZIC
c. Identify specific immune mediated neurological syndromes (stiff person syndrome, ataxia, limbic encephalitis) that are not exclusively linked to paraneoplastic aetiology	• GAD • Adenylate kinase 5 • Homer 3
Group II: abs against neuronal surface antigens	
a. Identify specific immune mediated neurological syndromes that are not exclusively linked to paraneoplastic aetiology, but that contribute to the pathogenesis of the non-paraneoplastic syndrome	• VGKC • AMPA-R • $GABA_B$-R • NMDA-R • Glycine-R
b. Abs present in cerebellar ataxia associated with small cell lung cancer or Hodgkin disease and has a presumably pathogenic impact on the paraneoplastic neurological syndrome	• VGCC • GluR1

nostic impact. Their detection helps to establish the diagnosis of paraneoplastic neurological syndromes and has even helped to identify new syndromes including chorea in patients with positive CV2 abs or mesodiencephalic encephalitis associated with Ma2 abs. Standardised tests are nowadays available for routine diagnostic purposes. The presence of group Ia abs strongly points to specific tumour types such as small cell lung cancer, breast, ovarian, or testicular cancer. The pathogenic link between other types of cancer and a paraneoplastic neurological syndrome has to be warranted by the demonstration of the respective antigens in the tumour tissue of the individual patient. Otherwise, a second neoplasm is more likely to trigger the paraneoplastic neurological syndrome. Abs (especially Hu, CV2 and amphiphysin associated with paraneoplastic cerebellar degeneration) may also be present in tumour patients without paraneoplastic neurological syndromes. Abs titres in these patients are usually lower than in patients presenting with paraneoplastic neurological syndromes. Diagnostic problems may then arise in patients with a long history of cancer who develop neurological disease. In these cases, other causes than paraneoplastic disease should be considered. This holds especially true if abs titres are low.

Hu antibodies

Hu abs are most frequently associated with small cell lung cancer and neuroblastoma. If the diagnosed tumour is extrathoracic, further tests are recommended to rule out a coexisting small cell lung cancer unless Hu reactivity can be demonstrated in the primary tumour. Hu abs may occur together with other antineuronal abs such as voltage gated calcium channels (VGCC), anti-amphiphysin, anti-CV2, anti-Ri, but they may exceptionally occur in systemic autoimmune disorders with neurological complications in the absence of an underlying neoplastic disease. Hu abs positive patients may present with cerebellar ataxia, encephalomyelitis, limbic encephalitis, brainstem encephalitis, epilepsia partialis continua, sensorimotor neuropathies with predominant motor involvement, sensory neuronopathy, neuromyotonia, and autonomic dysfunction including gastrointestinal motility disorders (7–9). Complete response of the tumour seems to have a favourable influence on the clinical course whereas concomitant immunotherapy does not seem to adversely affect tumour outcome by impairing the immune response to the tumour. Hu related antigenes are neuronal RNA-binding nuclear proteins that may be detected in both, the nucleus and the membrane of small cell lung cancer and neuroblastoma cells (10). The first and second RNA binding domains were identified as the main immunodominant regions. It has been hypothesised that surface binding-mediated pathogenic mechanisms are likely to account for the uncommonly good response of tumour specific and immunomodulatory therapy (11).

Yo antibodies

Yo abs strongly suggest ovarian (two-thirds) or breast (one-third) cancer. Yo abs were first identified in patients with ovarian cancer and paraneoplastic cerebellar degeneration (12, 13). The typical patient is a postmenopausal female developing subacute cerebellar and brainstem dysfunction within some days to weeks and clinical stabilisation after several weeks. Rarely, males with other tumours, for example lung cancer, may present with Yo abs. It is of interest, that neurological disease may precede tumour diagnosis by several years. In single cases, improvement of neurological symptoms after immunosuppressive therapy has been reported, but most patients do neither profit from tumour remission nor additional immunosuppressive therapy. Immunohistolo-

gical investigations show cytoplasmic staining of Purkinje cells. The antigens are two proteins of 34 and 62 kDa identified in Western blot analysis of protein extracts form Purkinje cells (12). In normal tissue, Yo expression is mainly restricted to cerebellar neurons including Purkinje cells, cells of the molecular layer and some neurons of the brain stem. Cdr34 and cdr62 have been identified as the coding genes. Cdr62 contains a zinc-finger domain and a leucine-zipper motif typical for proteins binding DNA as hetero- or homodimers (14). Cdr34 has the specialty to consist almost exclusively of tandem hexapeptide repeats of a special amino acid sequence. The latter results in a number of single Leu-Leu zipper elements. Yo abs are directed against an epitope located within the leucine-zipper domain of the cdr62 protein (15).

Ri antibodies

Ri abs are also known as ANNA-2 abs. They may be linked to cancer of the breast, lung, neck, fallopian tube, the bladder, stomach, thymus, non-Hodgkin lymphoma, and teratoma. In about half of the patients, tumour diagnosis is established at the onset of neurological impairment. Clinically, the typical syndrome associated with Ri abs is characterised by cerebellar ataxia and/or non-rhythmic axial and segmentary myoclonus plus fixation instability (myoclonus-opsoclonus syndrome). Other symptoms include brainstem encephalitis with diplopia, ophthalmoplegia, tinnitus, vertigo, nausea, laryngospasm myelopathy, peripheral neuropathy, cranial neuropathy, dystonia, Lambert-Eaton myasthenic syndrome and seizures. In patients with symptoms other than ataxia/myoclonus-opsoclonus, there is frequent evidence for additional concomitant antineuronal abs. The full-blown clinical syndrome can develop within a few hours. Neurological deficits improve substantially after tumour therapy. They are directed against adult RNA-binding proteins encoded by the NOVA-1 and NOVA-2 genes. Ri abs are mainly of the IgG type and are usually present in sera and cerebrospinal fluid (CSF) of affected patients. Anti-Ri reactivity may be identified in immunoblots of all regions of the CNS, but it predominates in basis pontis and dorsal mesencephalon.

CV2/CRMP5 antibodies

CV2/CRMP5 abs are – together with anti-Hu abs – considered the most frequent abs to be associated with small cell lung cancer. Some patients may even secret both, anti-CV2 and Hu abs. CV2/CRMP5 abs has also been observed in patients with malignant thymoma, breast cancer, uterine sarcoma, undifferentiated mediastinal cancer and head neck cancer. The latter patients are prone to develop additional myasthenic symptoms. In rare cases, CV2 abs may occasionally be present in tumour patients without neurological symptoms. Clinical features associated with CV2/CRMP5 include cerebellar degeneration, chorea, uveo/retinal symptoms, optic neuritis, encephalomyelitis including limbic encephalitis, obsessive-compulsive and behavioural disorders, mixed axonal and demyelinating sensory motor neuropathy (16). Interestingly, median survival is significantly longer in small cell lung cancer patients with CV2/CRMP5 abs than with Hu suggesting that the prognosis of the same type of tumour may depend on the associated onconeural abs (17). CV2 is a cytoplasmic 66-kD brain protein of the family of Ulip/CRMP proteins. It is encoded by the gene c-22. In *Caenorhabditis elegans* mutations of its homologue result in defective neuritic outgrowth and uncoordinated movements (18). Physiologically, the protein is expressed in the thymus. In the brain, it is predominantly found in white matter of adult rat brainstem, cerebellum, and spinal cord. Small cell lung cancer usually express CRMP5.

Amphiphysin antibodies

Amphiphysin abs can be associated with a variety of other autoabs (Hu, VGCC) and tumours (e.g. small cell lung cancer, adenocarcinoma of the lung, ovarian cancer) (2, 19). Occasionally, they occur in small cell lung cancer patients without paraneoplastic neurological syndromes or healthy controls. Isolated amphiphysin-IgG abs are predominantly found in females who suffer from myelitis or stiff person syndrome (20), but these abs may also be found in various other paraneoplastic syndromes such as limbic encephalitis, brainstem encephalitis, paraneoplastic cerebellar degeneration, opsoclonus, encephalomyelitis, Lambert-Eaton myasthenic syndrome, and sensorimotor neuropathy (2, 19). So, amphiphysin abs should not be considered specific for one type of tumour or one neurological syndrome. Patients may profit from early tumour therapy and immunomodulatory treatment.

Amphiphysin is a 128-kd protein found in synaptic vesicles at nerve terminals. It contains SH3 domains and is thought to function in clathrin-mediated endocytosis. Titres are usually high. The abs primarily recognise the C terminus of the protein, but some abs may also recognise other fragments of the molecule. CSF studies demonstrate anti-amphiphysin specific oligoclonal bands, although oligoclonal bands of total IgG may be absent.

Anti Ma2/anti-Ta antibodies

Anti Ma2/anti-Ta abs are usually present in young men with testicular germ cell tumours who present with a special type of encephalitis that differs from classical paraneoplastic limbic encephalitis with respect to the prominent limbic and diencephalic predilection sites (hippocampus, hypothalamus and brainstem). Clinically, patients present with seizures, vertical gaze paresis and hypokinesia (21, 22). The hypothalamic involvement is reflected by hypersomnia sometimes causing narcolepsy-cataplexy and low CSF hypocretin. About one-third of patients develop additional hormonal abnormalities. Encephalitic changes predominate in those regions of the brain known to express high concentrations of Ma proteins. CSF analysis may yield mild pleocytosis and increased protein concentrations. In rare cases, a clinical syndrome resembling motor neuron disease may evolve (22). Ma2 abs present in males older than 50 years or females may be contingent upon non-small cell lung cancer, breast, parotid gland, colon). An overlap with anti-Hu syndrome is possible. In two thirds of affected patients, neurological

symptoms precede tumour diagnosis. Ma2 positive limbic encephalitis has often a good prognosis. If the tumour cannot be treated, immunosuppressive therapy has to be applied. If other abs apart from Ma2 are found, the patient is more likely to have tumours other than testicular cancer, develop ataxia and to have a worse prognosis than patients with only anti-Ma2 abs. Ma2/Ta abs are usually present in serum and CSF as demonstrated by Western blot analysis and/or immunostaining. They are directed against Ma2 antigens expressed in neurons and testicular spermatogenic cells.

Group Ib (tumour-related onconeural abs): ZIC and SOX abs

Similar to group Ia abs, Ib abs recognise antigens expressed in the tumour and the CNS but in contrast to Ia abs, there is no evidence that the paraneoplastic neurological syndrome is directly mediated by these abs or any more complex immune response involving T lymphocytes. So, small cell lung cancer patients with paraneoplastic neurological syndromes do not show intrathecal synthesis of group Ib abs and their prevalence does normally not seem to differ between cancer patients with and without paraneoplastic neurological syndromes (with the exception of SOX abs in Lambert Eaton myasthenic syndrome (LEMS) that is contingent upon VGCC abs) (23, 24). SOX and ZIC2 abs have been identified by serological analysis of cDNA expression libraries from small cell lung cancer cell lines (25). SOX group B genes and ZIC2 encode DNA-binding proteins that regulate transcription of target genes in the presence of cofactors.

SOX

In a series of more than 212 unselected small cell lung cancer patients which included 35 patients with paraneoplastic neurological syndromes associated with classical onconeural abs, one-third showed SOX2 abs. Low tires of SOX2 abs may eventually be found in normal controls. In Lambert-Eaton myasthenic syndrome, the presence of SOX abs points to an underlying small cell lung cancer, but up to now, a specific paraneoplastic neurological syndrome could not been defined in patients with anti-SOX or anti-ZIC2 abs. The gene SOX family consists of groups A to H. SOX1, SOX2 and SOX3 are closely related: they are all encoded by genes belonging to group B1. SOX (as well as ZIC2) genes are expressed at early developmental stages in the embryonic nervous system, but are down-regulated in the adult brain. SOX1, 2, and 3 are expressed in up to 50% of small cell lung cancer. SOX group B antigens trigger serological responses in 30–40% of small cell lung cancer patients with SOX1 and/or SOX2 abs therefore being the main antigens eliciting anti-SOX responses. Tests using SOX1 as target antigen therefore seem the most robust for the identification of abs against SOX proteins.

ZIC

Most small cell lung cancer tumours express ZIC2. Clinically, there is no distinct clinical syndrome that could be assigned to ZIC2 abs and patients often have additional abs like Hu or CV2. Similarly to SOX, immunoreactivity of ZIC abs seems to be directed towards the conserved zinc-finger domains common to all ZIC proteins. ZIC positive sera normally recognise ZIC2 proteins, but some may also react with ZIC4 or ZIC1 as shown for a patient with non-paraneoplastic cerebellar disease (26).

Group Ic (non-paraneoplastic abs in CNS syndromes): abs against glutamic acid decarboxylase (GAD), adenylate kinase 5 (AK5) and Homer 3

Group Ic abs designate non-paraneoplastic neurological syndromes like stiff person syndrome, cerebellar ataxia and limbic encephalitis.

GAD antibodies

Glutamic acid decarboxylase (GAD) abs had first been detected in the CSF of a patient suffering from stiff person syndrome that is characterised by continuous motor unit activity in muscle at rest with abnormally enhanced exteroceptive reflexes (27, 28). This syndrome is usually associated with autoimmune disease like Insulin Dependent Diabetes Mellitus (IDDM), thyroiditis, autoimmune pluriglandular syndrome, vitiligo, pernicious anaemia, adrenal insufficiency or hypogammaglobulinaemia (27, 28). Interestingly, about 80% of IDDM patients have GAD abs but only a minority develop stiff person syndrome. Circulating GAD abs may also be associated with other neurological syndromes including cerebellar ataxia (stiff person syndrome plus cerebellar ataxia is also referred as Batten disease), palatal tremor, isolated downbeat nystagmus, periodic alternating nystagmus, limbic and brainstem encephalitis, myoclonic encephalopathy with multifocal myoclonus and opsoclonus, behavioural disturbance, various forms of epilepsy and autoimmune retinopathy (29–31). Intrathecal immunoglobulin synthesis is present in 86%–100% of patients with neurological symptoms. In patients without neurological symptoms, GAD abs titres may be as high as in neurological patients. Therefore, the link between GAD abs and CNS symptoms can only be assumed in patients with intrathecal abs synthesis. Otherwise, abs presence in peripheral blood just reflects autoimmune disease. GAD abs may be associated with anti-amphiphysin abs, antinuclear abs (ANA) or gastric parietal cell abs. The correlation of clinical severity and serum abs titres is not as tight as shown for other abs. In most cases of GAD positive neurological syndromes, there is no concomitant tumour. There have been only few reports on GAD abs in tumour patients such as thymoma or renal cell carcinoma (32) and tumour expression of the GAD antigen is restricted to single case reports. Therefore, the presence of GAD abs does not absolutely exclude any tumour association. The enzyme GAD is responsible for the synthesis of the inhibitory neurotransmitter γ-aminobutyric acid receptor (GABA). Like other abs implicated in stiff person syndrome such as amphiphysin and gephyrin, GAD abs appear to impair the

GABAergic system resulting in CNS hyperexcitability. In stiff person syndrome, GABA reduction in the motor cortex has been demonstrated with magnetic resonance spectroscopy. Furthermore, drugs that enhance GABA neurotransmission (diazepam, vigabatrin, and baclofen) provide mild to modest relief of clinical symptoms. Experimental studies demonstrated that CSF immunoglobulins from ataxic patients depress cerebellar GABAergic synaptic transmissions by a presynaptic mechanism *in vitro*. This effect is reversed by absorption of GAD-Abs using recombinant GAD. The injection into the lumbar paraspinal region induced continuous motor activity with repetitive discharges, abnormal exteroceptive reflexes, and increased excitability of anterior horn neurons (33). The 65 kDa isoform of GAD (GAD65) represents the major autoantigen in IDDM and in various neurological diseases, while the closely related isoform, GAD67, is less antigenic. Crystal structures for the two isoforms has shown that the N-, C- and middle domains (=identified previously as likely epitope regions) are closely associated within the GAD dimer. Two major epitope regions, ctc1 and ctc2, have been identified in the C-terminal domain of GAD65, that encompass N- and C-terminal residues, and middle and C-terminal residues respectively. These regions are highly flexible compared with the equivalent regions in GAD67, and T cell epitopes have been localised to the same surface region of GAD65.

Antigen adenylate kinase 5 (AK5) antibodies

AK5 abs are rather uncommon in cancer patients (independently of the presence of a paraneoplastic neurological syndrome), but have been reported in idiopathic forms of limbic encephalitis that did not improve under immunosuppressive therapy (34). The bad response to therapy may reflect the intracellular localisation of adenylate kinase 5 in the cytosol of brain neurons. The protein is critically involved in cell metabolism.

Homer 3 antibodies

Homer 3 abs were first demonstrated in a case of cerebellar ataxia accompanied by CSF pleocytosis, but no evidence for an underlying tumour (35). Indeed, abs directed to Homer 3 were absent in a cohort of patients with paraneoplastic cerebellar degeneration related to Hodgkin disease or small cell lung cancer and late onset cerebellar disease without pleocytosis (36). Homer 3 is expressed in the dendritic spines of cerebellar Purkinje cells. It binds to inositol 1, 4, 5 triphosphate receptors and the C-terminus of metabotropic glutamate receptor 1 (mGluR1). The complex is involved in postsynaptic calcium responses elicited by mGluR1 stimulation.

Group II: abs against neuronal surface antigens

Group II abs can be assigned to defined neurological syndromes that are not exclusively of paraneoplastic aetiology (37). Clinically, the associated neurological syndromes respond to therapeutic interventions. Group II abs target antigenic epitopes at the external surface of cell membranes. The antigens are usually located at pre- or postsynaptic sites. The clinical response to treatment is reflected by the level of the abs titre. Therefore, these abs are thought to have a direct pathogenic impact on the development of neurological disease.

Group IIa (markers for specific neurological syndromes): abs against voltage-gated potassium channels (VGKC), AMPA-, GABAb-, NMDA-, and glycine-receptors

Group IIa abs identify specific immune mediated neurological syndromes that are not exclusively linked to paraneoplastic aetiology. These abs are thought to contribute directly to the pathogenesis of the neurological syndrome.

Voltage-gated potassium channels (VGKC)

Initially, no tumour was reported in most of voltage-gated potassium channels (VGKC) abs positive cases. However, more recent studies report on an association with lung cancer, or thymoma in about one third of patients. Some non-paraneoplastic patients have evidence for concomitant autoimmune diseases. VGKC abs have been identified in patients with isolated limbic encephalitis or limbic encephalitis associated with neuromyotonia and autonomic dysfunction (commonly referred as Morvan syndrome) (38, 39). The typical patient with VGKC abs positive limbic encephalitis is male, presenting with the classical symptoms of limbic encephalitis with prominent memory loss, confusion, seizures, rapid eye movement (REM) sleep disorder, and low plasma sodium concentration (40). The clinical spectrum varies further from epilepsy, myasthenia gravis, Lambert-Eaton myasthenic syndrome, isolated or combined neuromyotonia (Isaac syndrome) to adult onset chronic intestinal pseudo-obstruction (41). Variable regimes of steroids, plasma exchange and intravenous immunoglobulin are associated with variable falls in serum VGKC-abs together with mild to marked improvement of cognitive deficits.

VGKC abs are thought to elicit hyperexcitability in both the peripheral and central nervous system. K(+) currents have been found to be suppressed in a neuroblastoma cell line that had been co-cultured with acquired neuromyotonia patients' immunoglobulin for several days, but this was not linked to any change in gating kinetics. Patch clamp studies show that antibodies may not directly block the kinetics of VGKCs, but may decrease channel density through increased degradation.

AMPA receptors

In limbic encephalitis patients negative for classical onconeural abs, abs against GluR1/2 subunits of the α-amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid (AMPA) receptor have been identified. The neurological syndrome is often of paraneoplastic origin (mainly associated with tumours of

the lung, breast, or thymus) and usually affects females. Many patients respond to immunotherapy or tumour therapy, but neurological relapses, without tumour recurrence, may be frequent and can influence the long-term outcome. AMPA receptors are composed of four types of subunits, designated as GluR1, GluR2, GluR3, and GluR4, which combine to form tetramers. Therefore, GluR antigens are located at the cell surface. Interestingly, GluR antigens do not seem to be expressed by the paraneoplastic tumours. Application of abs to cultures of neurons however significantly decrease the number of GluR-containing AMPA-receptor clusters at synapses with a decrease in overall AMPA-receptor cluster density. Abs removal reverses these effects (42).

Gamma-aminobutyric acid receptor (GABA receptor)

Abs to the B1 subunit of the inhibiting $GABA_B$-receptor have been isolated from the serum in paraneoplastic (e.g. small cell lung cancer) or non-paraneoplastic limbic encephalitis. Meanwhile, these abs are considered the most common abs present in limbic encephalitis with small cell lung cancer previously considered 'seronegative' (43). Typical clinical features comprise early and prominent seizures, acute episodes of respiratory crises, autonomic symptoms and insomnia ('agrypnia') (44). There is frequent evidence for additional GAD abs or even non-neurological abs although the frequency of GABA(B) receptor abs is low among GAD abs positive individuals. Moreover, the coincidence of both abs is only observed in the context of cancer. Patients may improve under immunotherapy and cancer treatment. GABA-receptor abs possess the ability of fixing complement: immunohistochemistry on brain sections of mice injected with patient IgG showed the simultaneous presence of bound human IgG and C5b-9 deposits on Purkinje cells and cerebellar granular layer. After incubation with anti-$GABA_B$-receptor abs, a marked reduction of receptor immunostaining was found with relative sparing of neuronal architecture (45).

NMDA receptor

About 60% of patients with neurological disease related to abs to NR1-NR2 heteromers of the ionotropic N-methyl D-aspartate (NMDA)-receptor have evidence of a tumour, most commonly ovarian teratoma (46). Recently, a potential relationship with *Mycoplasma pneumoniae* infections has been postulated in non-paraneoplastic cases (47). A severe encephalitis mainly affecting young females (but with a broad range of the age of onset) has been linked to NMDA-receptor abs (46). The clinical phenotype is characterised by fever, psychosis, anxiety and behavioural changes followed by seizures, impaired consciousness, memory deficits, aphasia, hypoventilation requiring mechanic ventilation, autonomic dysfunction, and dyskinesias (involuntary movements and facial dyskinesias that are refractory to anti-epileptic drugs). Anti-NMDA-receptor abs encephalitis is also increasingly recognised in children, comprising 40% of all cases. Younger patients are less likely to have tumours (48). The phenotype resembles the adult form, although dysautonomia and hypoventilation are less frequent or severe in children. Despite the severity of clinical symptoms during the acute phase, the prognosis is excellent: Almost 80% of patients recover fully or with minor residual impairment. Relapses usually related to a delay in tumour diagnosis may complicate the clinical course. Therefore, prompt diagnosis and treatment of the tumour is important. Immunotherapy alone does not produce comparable good results.

Post mortem investigations yielded Ig deposits in the hippocampus, extensive microgliosis, rare T-cell infiltrates, and neuronal degeneration predominantly involving, but not restricted to the hippocampus. Ovarian tumour tissue examined contained nervous tissue that strongly expressed NMDA-receptor subunits and reacts with patients' abs. The hypothesis of an abs mediated pathogenesis is also given support by the disappearance of abs with clinical improvement (49). These abs directed against NR1-NR2 heteromers of the NMDA-receptor belong to the immunoglobulin G1 subclass. They were also shown to activate complement on NMDA-receptor expressing human embryonic kidney cells (50). The conformal extracellular epitopes present in the NR1/NR2B heteromers of NMDA-receptor are expressed in the hippocampus/forebrain. Expression of functional heteromers (not single subunits) is required for abs binding (1). The target extracellular epitopes are not detectable by immunoblotting, and should not be confused with the linear epitopes of NR2B subunits (also known as epsilon2). It is currently speculated that NMDA-receptors in presynaptic GABAergic interneurons may rather be inhibited than stimulated by NMDA-receptor abs resulting in the disinhibition of postsynaptic glutamatergic transmission, excessive release of glutamate in prefrontal/ subcortical structures, and dysregulation of glutamate and dopamine transmission that might contribute to development of schizophrenia-like psychosis and bizarre dyskinesias (51).

Glycine receptor

Progressive encephalomyelitis with rigidity of limb and trunk and myoclonus (PERM), a special form of stiff person syndrome, is likely to be linked to abs against the postsynaptic glycine-receptor. The disorder may be associated with thymoma (52), but regarding the small number of reported cases, these data must be regarded preliminary. Clinical characteristics are rigidity of limb and trunk, myoclonus, spasms, hyperekplexia, brainstem symptoms and epilepsy (53). Some individuals respond to immunotherapy (53, 54). Glycine receptors act as ligand-gated chloride channels implicated in inhibitory neurotransmission mainly in spinal cord and brainstem. It has been hypothesised that abs might result in down-regulation of glycine receptor expression (53).

Group IIb: abs against voltage-gated calcium channels (VGCC) and metabotropic glutamate receptor type 1 (MGlu-R1)

Group IIb abs characterize cerebellar disease associated with small cell lung cancer or Hodgkin disease. They are consid-

ered to exert a presumably pathogenic impact on the paraneoplastic neurological syndrome.

Voltage-gated calcium channels (VGCC)

VGCC abs are found in about 85% of patients with Lambert-Eaton myasthenic syndrome. Fifty percent to 70% are of paraneoplastic aetiology and it has been reported in various tumour types (vocal cord carcinoma, large cell neuroendocrine carcinoma (LCNEC) of the lung, pulmonary squamous cell carcinoma), but the most frequent tumour associated is small cell lung cancer. Onset may vary from childhood to adult life; however, paraneoplastic cases usually start before the age of 30. Lambert-Eaton myasthenic syndrome is characterised by proximal muscle weakness initially affecting gait, autonomic symptoms (dry mouth, constipation, erectile failure), augmentation of strength during initial voluntary activation, and depressed tendon reflexes with post-tetanic potentiation (55, 56). VGCC autoabs titres do usually not correlate with electrophysiological disease severity across individuals but in longitudinal studies, there seems to be an inverse relation between abs titre and disease severity in Lambert-Eaton myasthenic syndrome. While VGCC abs can also be detected in about 40% of patients with paraneoplastic cerebellar degeneration associated with lung cancer, their titres are usually normal or only moderately increased in patients with late onset non-paraneoplastic cerebellar degeneration (57, 58). Low VGCC titres may also positive in rheumatoid arthritis and systemic lupus, but at lower titres. Nevertheless, the detection of VGCC abs is likely to indicate an underlying lung tumour. In single small cell lung cancer cases, limbic encephalitis has also been found to be associated with abs against N-type VGCC. In paraneoplastic Lambert-Eaton myasthenic syndrome, specific tumour therapy will often ameliorate the neurological disorder. Rapid diagnosis of Lambert-Eaton myasthenic syndrome can result in early detection of the underlying tumour. However, immunotherapy has not been found to improve cerebellar symptoms associated with VGCC abs (in contrast to other syndromes associated with abs to surface antigens). Regarding regenerative limitations within the CNS, this ineffectiveness is likely to result from irreversible cerebellar cell loss even at early stages of the immune process. VGCC have multiple physiological functions: the calcium influx through VGCCs regulates protein phosphorylation, gene expression, neurotransmitter release, firing patterns of action potential in dendritic regions of some neurons, growth cone elongation. VGCC are present throughout the nervous system. Their expression in motor nerve terminals explains their implication in Lambert Eaton myasthenic syndrome. In animals, chronic administration of plasma, serum or immunoglobulin G ('passive transfer' model) mimics the electrophysiological and ultrastructural findings seen in muscle biopsies of human Lambert-Eaton myasthenic syndrome. The reduction in amplitude of Ca^{2+} currents through P/Q-type channels is followed by 'unmasking' of an L-type Ca^{2+} current not normally found at the motor nerve terminal (59, 60). It is unclear what mechanisms underlie the development of this novel L-type Ca^{2+} current. The downregulation of VGCC leads to reduced acetylcholine release from motoneuron terminals thereby causing muscular weakness and autonomic dysfunction. Small cell lung cancer lines express many neuronal and neuroendocrine proteins including neuronal calcium channels of the Cav2 family (P/Q and N-type channels) (61). In Lambert-Eaton myasthenic syndrome, the S5-S6 linker regions in three of four domains could be specified as the immunodominant sites in the molecular structure of P/Q-type VGCC alpha1 subunit. P/Q type VGCCs are also important for the development and function of cerebellar Purkinje cells. Indeed, some patients with Lambert-Eaton myasthenic syndrome and small cell lung cancer actually develop additional cerebellar symptoms due to loss of VGCC as demonstrated by *post mortem* studies (62).

Metabotropic glutamate receptor type 1 (MGlu-R1)

Metabotropic glutamate receptor (MGlu-R1) abs have been identified in single patients with a history of Hodgkin disease who developed cerebellar symptoms several years after tumour diagnosis (63). Abs directed against the metabotropic mGluR1 can be isolated from serum and CSF. In classical paraneoplastic cerebellar degeneration, neurological symptoms usually precede tumour diagnosis. The long time interval between the occurrence of the tumour and the neurological deficits and the order of manifestation therefore questions a tight pathogenic link between GluR1 autoabs and the tumour.

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