Paraneoplastic and non-paraneoplastic autoimmunity to neurons in the central nervous system

Nico Melzer · Sven G. Meuth · Heinz Wiendl

Abstract Autoimmune central nervous system (CNS) inflammation occurs both in a paraneoplastic and non-paraneoplastic context. In a widening spectrum of clinical disorders, the underlying adaptive (auto) immune response targets neurons with a divergent role for cellular and humoral disease mechanisms: (1) in encephalitis associated with antibodies to intracellular neuronal antigens, neuronal antigen-specific CD8+ T cells seemingly account for irreversible progressive neuronal cell death and neurological decline with poor response to immunotherapy. However, a pathogenic effect of humoral immune mechanisms is also debated. (2) In encephalitis associated with antibodies to synaptic and extrasynaptic neuronal cell surface antigens, potentially reversible antibody-mediated disturbance of synaptic transmission and neuronal excitability occurs in the absence of excessive neuronal damage and accounts for a good response to immunotherapy. However, a pathogenic effect of cellular immune mechanisms is also debated. We provide an overview of entities, clinical hallmarks, imaging features, characteristic laboratory, electrophysiological, cerebrospinal fluid and neuropathological findings, cellular and molecular disease mechanisms as well as therapeutic options in these two broad categories of inflammatory CNS disorders.

Keywords Cancer · Autoimmunity · Neurons · Encephalitis · Antibodies · Cytotoxic T cells · Ion channels · Neurotransmitter receptors

Introduction

The human central nervous system (CNS) can be targeted by aberrant cellular and humoral immune responses, which can either be triggered by systemic infections, and vaccinations (“postinfectious/vaccinal autoimmune encephalitis”) and a variety of cancers (“paraneoplastic autoimmune encephalitis”) or occur without an (yet) identifiable cause (“non-paraneoplastic autoimmune encephalitis”) [25]. The scope of neurological disorders, in which such misguided adaptive immune responses are directed towards the oligodendrocyte and myelin-sheath is well described [24]. However, in a variety of immune-mediated CNS disorders, neurons seem to be targeted by adaptive cellular and humoral (auto) immune responses of both paraneoplastic and non-paraneoplastic origin [35]. Here, we summarize important clinical phenotypes together with their typical paraclinical measures, putative disease mechanisms, and therapeutic options in this emerging class of inflammatory CNS disorders.

Prerequisites for neuron-directed autoimmunity in the CNS

Antigen-specific cellular and humoral immune responses directed towards CNS neurons are believed to develop as a multi-step process [73]. Soluble or cell-bound neuronal or neuronal-like antigens are engulfed and presented in the context of MHC II and co-stimulatory molecules to CD4+ T cells by professional antigen-presenting cell (APCs)
within secondary lymphatic organs (e.g., cervical lymph nodes). This in turn permits CD4+ T cells via cytokine secretion and ligation of CD40 to license APCs to cross-present these antigens in the context of MHC I and co-stimulatory molecules to naive CD8+ T cells, which then become activated and may acquire cytotoxic effector functions (cellular effectors). A lack of such CD4+ T cell help usually results in anergy of CD8+ T cells. Depending on the local cytokine milieu mainly provided by CD4+ T cells, CD8+ T cells with different functional polarization may develop [86]. Tc1 cells are differentiated in the presence of IL-2 and IL-12, which induce the transcription factor T-bet. They produce IFN-γ and TNF-α and exert strong cytotoxicity. Tc2 cells are differentiated in the presence of IL-4 and IL-13 and exert a less robust cytotoxicity. Tc17 cells are differentiated in the presence of TGF-β and IL-6, which mainly induce the transcription factor RORγt. They produce IL-17 and have been reported to exert only weak cytotoxicity.

Naive B cells produce both IgM (and IgD) that are anchored in their plasma membrane and function as BCRs [48]. Naive B cells that encounter, ingest, and present their cognate so-called “thymus-dependent (TD) antigen” in the context of MHC II and co-stimulatory molecules to CD4+ T cells are in turn activated via cytokine secretion and ligation of CD40 and become antibody-secreting plasma cells (humoral effectors). Thereby, B cells can further diversify their Ig-genes by two DNA-modifying mechanisms [48]: somatic hypermutation and class switch recombination generate highly specific and adapted humoral responses. Somatic hypermutation introduces in a transcription-dependent manner non-templated point mutations in the variable (V) region of Ig genes, thereby enabling the selection of antibodies with increased affinity for the antigen. In contrast, class switch recombination modulates antibody effector function by replacing one constant (C) region with another, while retaining the binding specificity of the BCR. Depending on the cytokine milieu mainly provided by the CD4+ T cells, activated B cells undergo antibody class switching to produce IgG, IgA, or IgE antibodies [48]. Switch to IgG1 and IgG3 promoting complement activation and antibody-mediated cellular cytotoxicity by NK cells occurs in the presence of IFN-γ. In contrast, switch to IgG2, IgG4, and IgA promoting antigen-neutralizing effects occurs in the presence of IL-4 and IL-5. Although some pathogen-derived “thymus-independent (TI) antigens” may induce somatic hypermutation and class switch recombination in B cells independent from CD4+ T cell help, a lack of such help usually results in persistent secretion of complement-activating IgM (and IgD; [48]).

Following peripheral activation, both antibody-secreting plasma cells and cytotoxic CD8+ T cells (together with CD4+ T cells) may enter the CNS to attack neurons and cause functional and structural impairment [69, 97]. Moreover, under such inflammatory conditions, even antibodies produced in the periphery may permeate the blood–brain barrier (BBB) by various paracellular and transcellular mechanisms and thus contribute to neuron-directed immunity, whereas under physiological conditions, the BBB is usually impermeable for antibodies [23] (see Fig. 1).

In general, both effector arms of the adaptive immune response may be activated irrespective of the cellular localization of the neuronal antigen or its antigenic epitope (plasma membrane vs. interior cellular compartments). In terms of relevant effector mechanisms, plasma cell-derived antibodies usually recognize discontinuous conformational epitopes composed of segments of the respective neuronal plasma membrane protein antigen that are brought together in its three-dimensional structure and exposed on the neuronal plasma membrane. Antibodies may thus specifically impact the function and expression of these antigens. Whether antibodies may also bind to and impact the function or expression of intracellular neuronal antigens, either by passive uptake into the neuron or by active binding to intracellular antigens that are transiently exposed to the plasma membrane is currently a matter of debate [30, 96]. Moreover, peptides derived from both intracellular and plasma membrane neuronal antigens might potentially be recognized by antibodies when exposed on the surface membrane in complex with MHC I molecules, although this is usually performed by CD8+ T cells.

Cytotoxic CD8+ T cells usually recognize continuous linear peptide epitopes consisting of 8–10 amino acids that are derived from intracellular neuronal proteins by extensive antigen processing and presented in the context of MHC I molecules on the cell surface membrane. Whether peptides derived from neuronal surface membrane antigens are also presented to cytotoxic CD8+ T cells in the context of MHC I molecules is unclear at present. In both cases, CD8+ T cells cannot directly impact the function or expression of their cognate antigens, but recognize their expression by the respective neuron. This enables them to contribute to neuronal dysfunction and cell death by the antigen-dependent release of effector molecules (perforin, granzymes) from cytotoxic granules. Indeed, we could show that two separate functional consequences result from a direct cell-to-cell contact between antigen-presenting neurons and antigen-specific CD8+ T cells. (1) An immediate impairment of electrical signaling in single neurons and neuronal networks occurs as a result of massive shunting of the membrane capacitance after insertion of channel-forming perforin (and probably activation of other transmembrane conductances), which is paralleled by an increase of intracellular Ca2+ levels. (2) Antigen-dependent neuronal apoptosis may occur independently of...
perforin and members of the granzyme B cluster, suggesting that extracellular effects can substitute for intracellular delivery of granzymes by perforin. Thus, electrical silencing is an immediate consequence of MHC I-restricted interaction of CD8\(^{+}\) T cells with neurons. Of course, these changes in neuronal excitability are not induced specifically in response to a certain antigen, but apply to all antigen-presenting neurons encountered by activated cytotoxic CD8\(^{+}\) T cells [69, 71].

Paraneoplastic autoimmune encephalitis is probably mediated by cytotoxic CD8\(^{+}\) T cells specific for intracellular neuronal antigens

An ever-growing number of paraneoplastic CNS disorders are defined by the presence of IgG antibodies in the serum and CSF directed against intracellular neuronal antigens aberrantly expressed also by tumor cells (“onco-neuronal antibodies”) [67]. These tumors often contain neuronally differentiated tissue (germ cell tumors), express certain neuroendocrine peptides (SCLC, neuroblastoma), or occur in organs with a role in immune regulation (thymoma). However, due to the intracellular localization of the antigens, the humoral immune response is considered a non-pathogenic “epiphenomenon” solely indicating neuron-directed immunity and defining its antigen. In contrast, a variety of findings suggest a pathogenic role of cytotoxic CD8\(^{+}\) T cells for neuronal damage in these disorders: (1) neuronal damage often correlates with the number of CD8\(^{+}\) T cells, (2) CD8\(^{+}\) T cells are found in the CNS parenchyma in close spatial proximity to neuronal target cells, (3) CD8\(^{+}\) T cells show an activated phenotype with substantial expression of the effector molecules (perforin and granzymes) in cytoxic granules with a polar orientation towards the target cell membrane, (4) CD8\(^{+}\) T cells stain positive for CD107 indicating recent exocytosis of cytotoxic granules (i.e., degranulation), (5) neuronal target cells exhibit substantial cell surface expression of MHC I molecules allowing for cognate antigen-recognition by CD8\(^{+}\)
T cells, (6) CD8$^+$ T cells exhibit a restricted T cell receptor (TCR) repertoire (i.e., oligoclonal expansions) suggesting that they have expanded from a few precursors locally responding to a distinct neuronal antigen [6, 69]. These criteria, however, have not yet been demonstrated entirely for all entities.

In clinical terms, inflammatory CNS disorders associated with IgG antibodies against intracellular neuronal antigens are characterized by a multifocal presentation of CNS-related symptoms involving the neocortex, the limbic system, basal ganglia, brainstem, cerebellum, and spinal cord as well as PNS-related symptoms involving radices, plexus, and peripheral nerves in a variable extent (Table 1). The clinical presentation partially reflects the pattern of expression of the respective neuronal antigen: ANNA-1 targets nuclear ELAVL ("Hu") proteins expressed in central and peripheral neurons, and the corresponding clinical syndrome typically includes CNS and PNS manifestations [58]. In contrast, ANNA-2 targets nuclear NOVA-1 and -2 ("Ri") proteins expressed in central, but not peripheral neurons and the clinical syndrome is usually restricted to the CNS [75] (Table 1). MRI findings include T2/FLAIR hyperintense, occasionally contrast-enhancing lesions in the cortex, medial temporal lobes, basal ganglia, brainstem, cerebellum, and spinal cord. Inflammatory changes are usually found in CSF studies including lymphocytic pleocytosis, mildly elevated protein together with intrathecal IgG synthesis and oligoclonal bands, but normal glucose and lactate levels [19]. The disease entities usually exhibit a chronic progressive clinical course and poor response to immunotherapy, especially to antibody-depleting therapies. Even successful removal of the tumor considered to drive the pathogenic immune response is usually not associated with disease amelioration [19].

However, there exists a group of CNS disorders with antibodies against intracellular neuronal antigens located mainly at presynaptic (GAD65) or postsynaptic (GABA-RAP, Gephyrin) sites of inhibitory GABAergic and glycinergetic synapses, which less frequently associate with tumors. In these entities, there is often no evidence for cellular or humoral neuronal cytotoxicity, although some patients show neuroaxonal swelling, chromatolysis and vacuolization of neurons, microglial proliferation, as well as infiltration and apposition of cytotoxic CD8$^+$ T cells to neurons [6, 40]. Further, there are reports of potentially pathogenic humoral mechanisms probably targeting inhibitory CNS neuronal networks in anti-GAD encephalitis [29, 57, 61], but until now the specificity of possible pathogenic antibodies has not been elucidated. These findings together with the wide spectrum of clinical presentations suggest that anti-GAD encephalitis comprises of a quite heterogenous group of CNS disorders with regard to their etiologies and disease mechanisms.

**Paraneoplastic and non-paraneoplastic autoimmune encephalitis is probably mediated by antibodies to neuronal surface membrane antigens**

Autoimmune inflammatory CNS disorders associated with IgG antibodies in the serum and CSF directed against neuronal surface membrane antigens [54, 97] occur both in a paraneoplastic and non-paraneoplastic context. Tumors assumed to drive the pathogenic immune response usually contain neuronally differentiated tissue expressing the respective neuronal antigen or occur in organs with a role in immune regulation, such as the thymus.

Antibodies bind to synaptic and extra-synaptic ligand-and voltage-gated ion channels (Table 2) involved in excitatory (AMPA-, NMDA-, mGluR1-, mGluR5-, and nAch-receptors, VGCC, VGKC) and inhibitory (GABA$\text{A}_\text{B}$- and Glycine-receptors, VGKC) synaptic transmission and plasticity. Moreover, these antibodies also target neuronal membrane proteins implicated in clustering of voltage-gated potassium channels inside the synapse [leucine-rich glioma-inactivated 1 (LGI1)] or outside the synapse at the juxtaparanodal region of the node of Ranvier [contactin-2 and contactin-associated protein-like 2 (CASPR2)] thereby indirectly impacting neuronal excitability.

In principle, depending on the IgG subtype, antibodies may (1) specifically activate or block the function of their target molecules (GABA$\text{A}_\text{B}$-, Glycine- nAch-receptors, VGCC, VGKC), (2) crosslink and internalize the receptors (AMPA- and NMDA-receptors), (3) activate the complement cascade with subsequent formation of the terminal membrane attack complex and target cell lysis (probably mGluR1/5 receptors, VGCC, VGKC) and (4) activate Fc-receptors with subsequent antibody-dependent cell-mediated cytotoxicity (ADCC) mainly by NK cells [23]. However, the effector mechanisms involved in the pathogenic effect of the autoantibodies within the CNS are not yet fully understood. In fact, autoantibodies in anti-NMDA-R and -AMPA-R, GABA$\text{B}_\text{A}$-R encephalitis are of the IgG1 and IgG3 type and are thus capable of activating complement in the presence of patient plasma (containing high concentrations of complement factors). However, in none of the reported autopsy or biopsy studies complement depositions could be detected on neurons suggesting that in the presence of patient CSF (containing low concentrations of complement factors) these IgG1 and 3 autoantibodies do not lead to relevant complement activation [6, 32, 47, 50, 63, 93]. In contrast, autoantibodies in VGKC-complex encephalitis are predominantly of the IgG4 (and IgG1) type and thus are unable to activate complement in the presence of patient plasma. However, in the only biopsy study reported thus far, complement depositions could be detected on neurons in VGKC-complex encephalitis suggesting that in the presence of patient CSF these IgG4 (or
| Entity | Patients | Triggers | Clinical hallmarks | Imaging | Electrophysiology | Laboratory |
|--------|----------|----------|-------------------|---------|-------------------|------------|
| ANNA-1 (Hu) encephalitis | Age 30–80 years (median 60 years), gender male 75 %, ANPR >500 | Tumors: lung (SCLC in adults), neuroendocrine tissue (neuroblastoma in children), rarely thymus (thymoma) | Neocortical and limbic encephalitis, brainstem encephalitis, cerebellitis, myelitis, cranial neuropathy, radiculopathy, plexopathy, peripheral (sensory, motor, sensorimotor, autonomic) neuropathy | MRE: T2/FLAIR hyperintense signal, occasionally Gd-enhancement and atrophy in cortex, medial temporal lobes, brainstem, cerebellum or spinal cord FDG-PET: focal hypermetabolism at early disease-stages, focal hypometabolism at late disease-stages | EEG: 1. focal or widespread interictal and ictal epileptiform activity, 2. focal or generalized slowing | Anti-neuronal nuclear IgG1/3 antibody type 1 (ANNA-1; anti-Hu antibody) in serum and CSF targeting nuclear ELAVL ("Hu") proteins expressed in central and peripheral neurons and tumor cells and implicated in neuronal post-transcriptional RNA regulation ("onco-neuronal" antibodies) |
| ANNA-2 (Ri) encephalitis | Age 50–80 years (median 65 years), gender female 80 %, ANPR 100 | Tumors: lung (SCLC), breast | Neocortical and limbic encephalitis, brainstem encephalitis, cerebellitis, myelitis | MRE: T2/FLAIR hyperintense signal, occasionally Gd-enhancement and atrophy in cortex, medial temporal lobes, brainstem, cerebellum or spinal cord FDG-PET: focal hypermetabolism at early disease-stages, focal hypometabolism at late disease-stages | EEG: 1. focal or widespread interictal and ictal epileptiform activity, 2. focal or generalized slowing | Anti-neuronal nuclear IgG1/3 antibody type 2 (ANNA-2; anti-Ri antibody) in serum and CSF targeting nuclear NOVA-1 and –2 ("Ri") proteins expressed in central but not peripheral neurons and tumor cells and implicated in regulation of alternative splicing of neuronal RNA encoding synaptic proteins (N-, P/Q-type Ca^{2+} channels; "onco-neuronal" antibodies) |
| ANNA-3 encephalitis | Age 10–85 years (median 60 years), gender female 50 %, ANPR 10 | Tumors: lung (SCLC, adenocarcinoma), esophagus (adenocarcinoma) | Limbic encephalitis, brainstem encephalitis, cerebellitis, myelitis, peripheral (sensory, sensorimotor) neuropathy | MRE: T2/FLAIR hyperintense signal, occasionally Gd-enhancement and atrophy in cortex, medial temporal lobes, brainstem, cerebellum or spinal cord FDG-PET: focal hypermetabolism at early disease-stages, focal hypometabolism at late disease-stages | EEG: 1. focal or widespread interictal and ictal epileptiform activity, 2. focal or generalized slowing | Anti-neuronal nuclear IgG1/3 antibody type 3 (ANNA-3) in serum and CSF targeting a nuclear 170 kDa protein of unknown molecular identity expressed in central (Parkinson neurons) and peripheral neurons and tumor cells ("onco-neuronal" antibodies) |
| AGNA (SOX-1) encephalitis | –, ANPR 100 | Tumors: lung (SCLC) | Limbic encephalitis, brainstem encephalitis, cerebellitis, peripheral neuropathy Lambert-Eaton myasthenic syndrome (LEMS) | MRE: T2/FLAIR hyperintense signal, occasionally Gd-enhancement and atrophy in medial temporal lobes, brainstem or cerebellum FDG-PET: focal hypermetabolism at early disease-stages, focal hypometabolism at late disease-stages | EEG: 1. focal or widespread interictal and ictal epileptiform activity, 2. focal or generalized slowing Nerve conduction studies: predominantly axonal sensory, motor or sensorimotor neuropathy EMG: decrement of compound muscle action potential on 2–5/s repetitive nerve stimulation, increment of compound muscle action potential on 30–50/s repetitive nerve stimulation or "post-tetanic" stimulation | Anti-glial/neuronal nuclear IgG1/3 antibody (AGNA) in serum and CSF targeting nuclear SOX1 protein expressed predominantly in developing and adult cerebellar Bergmann glia cells, central and peripheral neurons and tumor cells and implicated in transcription regulation during neuronal development ("onco-neuronal" antibodies) |
| Entity                  | Patients | Triggers                                                                 | Clinical hallmarks                                                                 | Imaging                                                                 | Electrophysiology                                                                 | Laboratory                                                                 |
|------------------------|----------|---------------------------------------------------------------------------|------------------------------------------------------------------------------------|----------------------------------------------------------------------------|---------------------------------------------------------------------------------|--------------------------------------------------------------------------------|
| Anti-Ma1/Ma2 encephalitis | Age: 40–70 years (median 55 years), gender male 75 %, ANPR 75 | Tumors: women with non-germ cell tumors of ovary, breast, colon, lung (combined anti-Ma1/Ma2-encephalitis), men with germ cell tumors of testis (pure anti-Ma2-encephalitis) | Anti-Ma1/Ma2 encephalitis: limbic encephalitis, diencephalitis, brainstem encephalitis and cerebellitis Anti-Ma2 encephalitis: limbic encephalitis, diencephalitis, brainstem encephalitis without cerebellitis | MRE: T2/FLAIR hyperintense signal, occasionally Gd-enhancement and atrophy in medial temporal lobes, diencephalon, brainstem or cerebellum FDG-PET: focal hypermetabolism at early disease-stages, focal hypometabolism at late disease-stages | EEG: 1. focal or widespread interictal and ictal epileptiform activity, 2. focal or generalized slowing | Anti-Ma (PNMA1) and/or Anti-Ma2 (PNMA2) IgG1/3 antibody in serum and CSF targeting nucleolar/subnuclear Ma1 (PNMA1) and Ma2 (PNMA2) proteins expressed in central neurons and in tumor cells and implicated in transcription regulation ("onco-neuronal" antibodies) |
| Anti-CV2 (CRMP-3) encephalitis | Age: 50–75 years (median 60 years), gender female 60 %, ANPR 30 | Tumors: lung (SCLC), thymus (thymoma), kidney (carcinoma), thyroid gland (carcinoma) | Uveitis, retinitis, optic neuritis, limbic encephalitis, cerebellitis, myelitis peripheral (sensory, motor, sensorimotor) neuropathy neuromyelitis optica-like clinical phenotype (optic neuritis + myelitis) | MRE: T2/FLAIR hyperintense signal, occasionally Gd-enhancement and atrophy in optic nerve, medial temporal lobes, cerebellum or spinal cord FDG-PET: focal hypermetabolism at early disease-stages, focal hypometabolism at late disease-stages | EEG: 1. focal or widespread interictal and ictal epileptiform activity, 2. focal or generalized slowing | Nerve conduction studies: axonal and demyelinating sensory, motor or sensorimotor neuropathy Anti-collapsin response-mediated protein 3 IgG1/3 antibody (CRMP-3-IgG) in serum and CSF targeting cytoplasmic collapsin response-mediated protein 3 expressed in a subpopulation of oligodendrocytes and central neurons, Schwann cells and peripheral neurons and tumor cells and implicated in axon guidance, synaptic organization and other cellular responses ("onco-neuronal" antibodies) |
| Anti-CRMP-5 encephalitis | Age: 50–75 years (median 60 years), gender female 60 %, ANPR 150 | Tumors: lung (SCLC), thymus (thymoma), kidney (carcinoma), thyroid gland (carcinoma) | Optic neuritis with and without retinitis and other cranial neuropathies, neocortical and limbic encephalitis, "basal ganglionitis", cerebellitis, myelitis, radiculopathy, plexopathy, peripheral (sensory, motor, sensorimotor, autonomic) neuropathy, myasthenia gravis (MG), Lambert-Eaton myasthenic syndrome (LEMS), neuromyotonia neuromyelitis optica-like clinical phenotype (optic neuritis + myelitis) | MRE: T2/FLAIR hyperintense signal, occasionally Gd-enhancement and atrophy in optic and other cranial nerves, neocortex, medial temporal lobes, basal ganglia, cerebellum or spinal cord FDG-PET: focal hypermetabolism at early disease-stages, focal hypometabolism at late disease-stages | EEG: 1. focal or widespread interictal and ictal epileptiform activity, 2. focal or generalized slowing | Nerve conduction studies: axonal and demyelinating sensory, motor or sensorimotor neuropathy Anti-collapsin response-mediated protein 5 IgG1/3 antibody (CRMP-5-IgG) in serum and CSF targeting cytoplasmic collapsin response-mediated protein 5 expressed in central and peripheral neurons including synapses and tumor cells and implicated in axon guidance, synaptic organization and other cellular responses ("onco-neuronal" antibodies) |
| Entity                  | Patients | Triggers                                      | Clinical hallmarks                                      | Imaging                                   | Electrophysiology                                      | Laboratory                                                                 |
|-------------------------|----------|----------------------------------------------|---------------------------------------------------------|-------------------------------------------|--------------------------------------------------------|---------------------------------------------------------------------------|
| Anti-PCA-1 (Yo) encephalitis | Age 60–70 years (median 65 years), gender female 90 %, ANPR 150 | Tumors: breast, ovary, fallopian tube, endometrium     | Cerebellitis, brainstem encephalitis, myelitis, peripheral (sensory, motor, sensorimotor, autonomic) neuropathy | MRE: T2/FLAIR hyperintense signal, occasionally Gd-enhancement and atrophy in cerebellum, brainstem and spinal cord FDG-PET: focal hypermetabolism at early disease-stages, focal hypometabolism at late disease-stages | EEG: Generalized slowing or normal Nerve conduction studies; predominantly axonal sensory, motor or sensorimotor neuropathy | Parkinje cell cytoplasmic IgG1/3 autoantibody type 1 (PCA-1; anti-Yo antibody) in serum and CSF targeting cytoplasmic CDR2 and CDR62 ("Yo") proteins expressed in central and peripheral neurons especially cerebellar Parkinje neurons and tumors cells and implicated in downregulation of transcription via inhibition of c-Myc ("onco-neuronal" antibodies) |
| Anti-PCA-2 encephalitis  | Age 45–85 years (median 60 years), gender female 70 %, ANPR 10 | Tumors: lung (SCLC)                                    | Limbic encephalitis, brainstem encephalitis, cerebellitis, peripheral neuropathy | MRE: T2/FLAIR hyperintense signal, occasionally Gd-enhancement and atrophy in medial temporal lobes, brainstem or cerebellum FDG-PET: focal hypermetabolism at early disease-stages, focal hypometabolism at late disease-stages | EEG: 1. focal or widespread interictal and ictal epileptiform activity, 2. focal or generalized slowing Nerve conduction studies; predominantly axonal sensory, motor or sensorimotor neuropathy | Parkinje cell cytoplasmic IgG1/3 autoantibody type 2 (PCA-2) in serum and CSF targeting a cytoplasmic 280 kDa protein of unknown molecular identity expressed in central and peripheral neurons especially cerebellar Parkinje neurons and tumors cells ("onco-neuronal" antibodies) |
| Anti-PCA-Tr encephalitis | Age 15–70 years (median 60 years), gender male 75 %, ANPR 120 | Tumors: Hodgkin lymphoma, non-Hodgkin lymphoma, occasionally solid tumors (Limbic encephalitis), cerebellitis | MRE: T2/FLAIR hyperintense signal, occasionally Gd-enhancement and atrophy in cerebellum FDG-PET: focal hypermetabolism at early disease-stages, focal hypometabolism at late disease-stages | EEG: generalized slowing or normal | Parkinje cell cytoplasmic IgG1/3 autoantibody type Tr (PCA-Tr) in serum and CSF targeting Delta/Notch-like epidermal growth factor-related receptor (DNER) expressed in central neurons especially in cerebellar Parkinje neurons and occasionally in tumor cells (Reed-Sternberg cells) and implicated in neuron–glia interactions through notch signaling ("onco-neuronal" antibodies) |
| Anti-amphiphysin encephalitis | Age 50–80 years (median 65 years), gender female 60 %, ANPR 100 | Tumors: lung (SCLC, non-SCLC), breast, melanoma         | Limbic encephalitis, cerebellitis, myelitis, stiff-person syndrome, radiculopathy, plexopathy, peripheral (sensory, motor, sensorimotor) neuropathy | MRE: usually normal, occasionally T2/FLAIR hyperintense signal, Gd-enhancement and atrophy in medial temporal lobes, cerebellum and spinal cord | EEG: Usually normal, occasionally focal or generalized epileptiform activity and slowing Nerve conduction studies; predominantly axonal sensory, motor or sensorimotor neuropathy EMG: excessive startle response, continuous involuntary motor activity in agonistic and antagonistic muscles | Anti-Amphiphysin IgG antibody in serum and CSF targeting cytoplasmic amphiphysin expressed in central and peripheral neurons (presynaptic terminals) and in tumor cells and implicated in retrieving vesicle membranes from the axon terminal’s plasma membrane after depolarization-induced exocytosis of neurotransmitter ("onco-neuronal" antibodies) |
| Entity                                | Patients | Triggers                                                                 | Clinical hallmarks                                                                 | Imaging                                                                 | Electrophysiology                                                                 | Laboratory                                                                 |
|---------------------------------------|----------|--------------------------------------------------------------------------|----------------------------------------------------------------------------------|------------------------------------------------------------------------|--------------------------------------------------------------------------------|--------------------------------------------------------------------------------|
| Anti-GAD 65 encephalitis              |          | Tumors (occasionally): lung (SCLC, non-SCLC), thymus (thymoma), colon, pancreas, breast, thyroid, and renal cell carcinoma | Limbic encephalitis, epilepsy, basal ganglionitis, brainstem encephalitis, cerebellitis, myelitis, stiff-person syndrome, Progressive Encephalomyelitis with Rigidity and Myoclonus (PERM) stiffness/rigidity, excessive startle, brainstem dysfunction (anti-GAD 65 IgG antibody titer usually >2000 U/ml in RIA) Autoimmune diabetes mellitus (anti-GAD 65 IgG antibody titer usually <20 U/ml in RIA) | MRI: usually normal, occasionally T2/FLAIR hyperintense signal, Gd-enhancement and atrophy in medial temporal lobes, brainstem, cerebellum and spinal cord | EEG: Usually normal, occasionally focal or generalized epileptiform activity and slowing EMG: excessive startle response, continuous involuntary motor activity in agonistic and antagonistic muscles | Anti-GAD 65 IgG antibody in serum (>20,00 U/ml) and CSF, usually with intrathecal anti-GAD 65 IgG synthesis targeting the cytoplasmic 65 kDa isoform of glutamic acid decarboxylase expressed in central GABAergic neurons (presynaptic terminals), pancreatic islet cells and occasionally tumor cells and implicated in converting excitatory neurotransmitter glutamate to inhibitory neurotransmitter GABA (occasionally "onco-neuronal" antibodies) |
| Anti- GABA<sub>A</sub>-receptor associated protein encephalitis |          |                                                                         | Neocortical encephalitis, epilepsy, cerebellitis, stiff-person syndrome            | --                                                                     | EMG: continuous involuntary motor activity in agonistic and antagonistic muscles | Anti-GABARAP IgG antibody in serum and CSF targeting cytoplasmic and membrane GABARAP expressed in central neurons (postsynaptic density of GABAergic synapses) and implicated in clustering and anchoring GABA<sub>A</sub>-receptors in the postsynaptic membrane by facilitating binding to the cytoskeleton |
| Anti-gephyrin encephalitis            |          | Tumor: undifferentiated mediastinal carcinoma                           | Stiff-person syndrome                                                              | MRI: normal                                                            | EMG: continuous involuntary motor activity in agonistic and antagonistic muscles | Anti-gephyrin IgG antibody in serum and CSF targeting cytoplasmic gephyrin protein expressed in central neurons (postsynaptic density of GABAergic and glycinerergic synapses) and implicated in clustering and anchoring GABA<sub>A</sub>- and glycine receptors in the postsynaptic membrane by facilitating binding to the cytoskeleton |
Table 1 continued

| Entity | Patients | CSF | Neuropathology | Putative disease mechanisms | Therapy | Disease course and prognosis | References |
|--------|----------|-----|----------------|-----------------------------|---------|----------------------------|------------|
| ANNA-1 (Hu) encephalitis | Age 30–80 years (median 60 years), gender male 75 %, ANPR >500 | Lymphocytic pleocytosis (median 3/μL, range 1–8/μL), normal glucose and lactate, mildly elevated protein (median 78 mg/dL, range 49–135 mg/dL), intrathecal IgG synthesis and OCB | Inflammatory infiltrates (perivascular CD4+ T cells and B cells, parenchymal CD8+ T cells), glia, microglia activation, neuronal loss and neuronophagia | Neuronal cell death mediated by neuronal-antigen specific cytoxic CD8+ T cells | Immunotherapy: 1. GCS together with steroid-sparing agents, IVIG, PE/IA, 2. rituximab, cyclophosphamide; Tumor-therapy: (operation, radiation, chemotherapy) | Chronic disease course: usually poor response to immunotherapy and tumor-therapy | [1, 33, 40, 49, 67, 79, 83, 85, 87] |
| ANNA-2 (Ri) encephalitis | Age 50–80 years (median 65 years), gender female 80 %, ANPR 100 | Lymphocytic pleocytosis (median 5/μL, range 1–15/μL), normal glucose and lactate, mildly elevated protein (median 55 mg/dL, range 39–415 mg/dL), intrathecal IgG synthesis and OCB | Inflammatory infiltrates (perivascular CD4+ T cells and B cells, parenchymal CD8+ T cells and macrophages), glia, microglia activation, neuronal loss and neuronophagia | Neuronal cell death mediated by neuronal-antigen specific cytoxic CD8+ T cells | Immunotherapy: 1. GCS together with steroid-sparing agents, IVIG, PE/IA, 2. rituximab, cyclophosphamide; Tumor-therapy: (operation, radiation, chemotherapy) | Chronic disease course: usually poor response to immunotherapy and tumor-therapy | [37, 59, 67, 75, 79, 83, 85] |
| ANNA-3 encephalitis | Age 10–85 years (median 60 years), gender female 50 %, ANPR 10 | Lymphocytic pleocytosis, normal glucose and lactate, mildly elevated protein, intrathecal IgG synthesis and OCB | – | Presumably neuronal cell death mediated by neuronal-antigen specific cytoxic CD8+ T cells | Immunotherapy: 1. GCS together with steroid-sparing agents, IVIG, PE/IA, 2. rituximab, cyclophosphamide; Tumor-therapy: (operation, radiation, chemotherapy) | Chronic disease course: usually poor response to immunotherapy and tumor-therapy | [12, 37, 67, 83, 85] |
| AGNA (SOX-1) encephalitis | Age 50–75 years (median 60 years), gender male 75 %, ANPR 75 | Lymphocytic pleocytosis, normal glucose and lactate, mildly elevated protein, intrathecal IgG synthesis and OCB | – | Presumably neuronal cell death mediated by neuronal-antigen specific cytoxic CD8+ T cells | Immunotherapy: 1. GCS together with steroid-sparing agents, IVIG, PE/IA, 2. rituximab, cyclophosphamide; Tumor-therapy: (operation, radiation, chemotherapy) | Chronic disease course: usually poor response to immunotherapy and tumor-therapy | [36, 37, 67, 79, 83, 85, 92] |
| Anti-Ma1/Ma2 encephalitis | Age 40–70 years (median 55 years), gender male 75 %, ANPR 75 | Lymphocytic pleocytosis (median 3/μL, range 1–20/μL), normal glucose and lactate, mildly elevated protein (median 53 mg/dL, range 39–70 mg/dL), intrathecal IgG synthesis and OCB | Inflammatory infiltrates (perivascular CD4+ T cells and B cells, parenchymal CD8+ T cells and macrophages), glia, microglia activation, neuronal loss and neuronophagia | Neuronal cell death mediated by neuronal-antigen specific cytoxic CD8+ T cells | Immunotherapy: 1. GCS together with steroid-sparing agents, IVIG, PE/IA, 2. rituximab, cyclophosphamide; Tumor-therapy: (operation, radiation, chemotherapy) | Chronic disease course: usually poor response to immunotherapy and tumor-therapy | [16, 17, 37, 39, 67, 79, 82, 83, 85, 98] |
| Anti-CV2 (CRMP-3) encephalitis | Age 50–75 years (median 60 years), gender female 60 %, ANPR 30 | Lymphocytic pleocytosis (8–70/μL), normal glucose and lactate, mildly elevated protein (47–400 mg/dL), intrathecal IgG synthesis and OCB | Inflammatory infiltrates (perivascular CD4+ T cells and B cells, parenchymal CD8+ T cells), glia, microglia activation, neuronal loss and neuronophagia | Neuronal cell death mediated by neuronal-antigen specific cytoxic CD8+ T cells | Immunotherapy: 1. GCS together with steroid-sparing agents, IVIG, PE/IA, 2. rituximab, cyclophosphamide; Tumor-therapy: (operation, radiation, chemotherapy) | Chronic disease course: usually poor response to immunotherapy and tumor-therapy | [2, 41–43, 67, 79, 83] |

Lymphocytic pleocytosis, normal glucose and lactate, mildly elevated protein (median 78 mg/dL, range 49–135 mg/dL), intrathecal IgG synthesis and OCB.

Chronic disease course: usually poor response to immunotherapy and tumor-therapy.

References: [1, 33, 40, 49, 67, 79, 83, 85, 87, 37, 59, 67, 75, 79, 83, 85, 36, 37, 67, 79, 83, 85, 92, 16, 17, 37, 39, 67, 79, 82, 83, 85, 98, 2, 41–43, 67, 79, 83].
| Entity | Patients | CSF | Neuropathology | Putative disease mechanisms | Therapy | Disease course and prognosis | References |
|--------|----------|-----|----------------|-----------------------------|---------|-------------------------------|------------|
| Anti-CRMP-5 encephalitis | Age 50–75 years (median 60 years), gender female 60 %, ANPR 150 | Lymphocytic pleocytosis (8–370/μl), normal glucose and lactate, mildly elevated protein (47–400 mg/dL), intrathecal IgG synthesis and OCB | Inflammatory infiltrates (perivascular CD4⁺ T cells and B cells, parenchymal CD8⁺ T cells), gliosis, microglia activation, neuronal loss and neuronophagia | Neuronal cell death mediated by neuronal-antigen specific cytotoxic CD8⁺ T cells | Immunotherapy: 1. GCS together with steroid-sparing agents, IVIG, PE/IA, 2. rituximab, cyclophosphamide; Tumor-therapy: (operation, radiation, chemotherapy) | Chronic disease course: usually poor response to immunotherapy and tumor-therapy |
| Anti-PCA-1 (Yo) encephalitis | Age 60–70 years (median 65 years), gender female 90 %, ANPR 150 | Lymphocytic pleocytosis (median 4/μl, range 1–22/μl), normal glucose and lactate, mildly elevated protein (median 54 mg/dL, range 36–88 mg/dL), intrathecal IgG synthesis and OCB | Inflammatory infiltrates (perivascular CD4⁺ T cells and B cells, parenchymal CD8⁺ T cells and macrophages), gliosis, microglia activation, neuronal loss and neuronophagia | Neuronal cell death mediated by neuronal-antigen specific cytotoxic CD8⁺ T cells | Immunotherapy: 1. GCS together with steroid-sparing agents, IVIG, PE/IA, 2. rituximab, cyclophosphamide; Tumor-therapy: (operation, radiation, chemotherapy) | Chronic disease course: usually poor response to immunotherapy and tumor-therapy |
| Anti-PCA-2 encephalitis | Age 45–85 years (median 60 years), gender female 70 %, ANPR 10 | Lymphocytic pleocytosis normal glucose and lactate, mildly elevated protein, intrathecal IgG synthesis and OCB | – | Neuronal cell death mediated by neuronal-antigen specific cytotoxic CD8⁺ T cells | Immunotherapy: 1. GCS together with steroid-sparing agents, IVIG, PE/IA, 2. rituximab, cyclophosphamide; Tumor-therapy: (operation, radiation, chemotherapy) | Chronic disease course: usually poor response to immunotherapy and tumor-therapy |
| Anti-PCA-Tr encephalitis | Age 15–70 years (median 60 years), gender male 75 %, ANPR 120 | Lymphocytic pleocytosis (median 7/μl, range 3–10/μl) normal glucose and lactate, mildly elevated protein (median 41 mg/dL, range 25–72 mg/dL), usually no intrathecal IgG synthesis or OCB | Presumably neuronal cell death mediated by neuronal-antigen specific cytotoxic CD8⁺ T cells | Neuronal cell death and functional impairment mediated by neuronal-antigen specific cytotoxic CD8⁺ T cells alternatively: Binding to the amphiphysin protein and internalization of the IgG antibody into the presynaptic ending with disturbance of GABAergic > glutamatergic synaptic transmission | Immunotherapy: 1. GCS together with steroid-sparing agents, IVIG, PE/IA, 2. rituximab, cyclophosphamide; Tumor-therapy: (operation, radiation, chemotherapy) | Usually chronic disease course with poor response to immunotherapy and tumor-therapy, a subset of patients may stabilize or improve with eradication of the PCA-Tr antibody following successful tumor-therapy |
| Anti-amphiphysin encephalitis | Age 50–80 years (median 65 years), gender female 60 %, ANPR 100 | Lymphocytic pleocytosis (median 22/μl, range 2–42/μl) normal glucose and lactate, mildly elevated protein (median 104 mg/dL, range 57–151 mg/dL), intrathecal IgG synthesis and OCB | Inflammatory infiltrates (perivascular CD4⁺ T cells and B cells, parenchymal CD8⁺ T cells and macrophages), gliosis, microglia activation, neuronal loss and neuronophagia | Neuronal cell death and functional impairment mediated by neuronal-antigen specific cytotoxic CD8⁺ T cells alternatively: Binding to the amphiphysin protein and internalization of the IgG antibody into the presynaptic ending with disturbance of GABAergic > glutamatergic synaptic transmission | Immunotherapy: 1. GCS together with steroid-sparing agents, IVIG, PE/IA, 2. rituximab, cyclophosphamide; Tumor-therapy: (operation, radiation, chemotherapy) | Chronic disease course: usually poor response to immunotherapy and tumor-therapy |
| Entity                          | Patients                                                                 | CSF                                      | Neuropathology                                                                 | Putative disease mechanisms                                                                 | Therapy                                                                 | Disease course and prognosis                        | References                                      |
|-------------------------------|--------------------------------------------------------------------------|------------------------------------------|--------------------------------------------------------------------------------|---------------------------------------------------------------------------------------------|--------------------------------------------------------------------------|-------------------------------------------------|-------------------------------------------------|
| Anti-GAD 65 encephalitis      | Age 15–80 years (median 60 years), gender female 80 %, ANPR 200          | Lymphocytic pleocytosis, normal glucose and lactate, mildly elevated protein intrathecal IgG synthesis and OCB | Inflammatory infiltrates (perivascular CD4<sup>+</sup> T cells and B cells, parenchymal CD8<sup>+</sup> T cells and macrophages), gliosis, microglia activation, neuronal loss and neuronophagia | Neuronal cell death and functional impairment mediated by neuronal-antigen specific cytotoxic CD8<sup>+</sup> T cells | Immunotherapy: 1. GCS together with steroid-sparing agents, IVIG, PE/IA, 2. rituximab, cyclophosphamide; Tumor-therapy: occasionally | Chronic disease course: usually poor response to immunotherapy (and tumor-therapy) | [60, 67, 77, 79, 83, 84, 89, 90] |
| Anti-GABA<sub>A</sub>- A-receptor-associated protein encephalitis | ANPR 20                                                                 | –                                        | –                                                                              | Neuronal cell death and functional impairment mediated by neuronal-antigen specific cytotoxic CD8<sup>+</sup> T cells alternatively: binding to the GABARAP and internalization of the IgG antibody into the postsynaptic density, impairment of GABA<sub>A</sub>-receptor clustering and disturbance of GABAergic synaptic transmission | Immunotherapy: 1. GCS together with steroid-sparing agents, IVIG, PE/IA, 2. rituximab, cyclophosphamide | –                                               | [80]                                           |
| Anti-gephyrin encephalitis    | ANPR 1                                                                   | Normal                                   | –                                                                              | Neuronal cell death and functional impairment mediated by neuronal-antigen specific cytotoxic CD8<sup>+</sup> T cells alternatively: binding to the gephyrin protein and internalization of the IgG antibody into the postsynaptic density, impairment of GABA<sub>A</sub>- and glycine-receptor clustering and disturbance of GABAergic and glycineergic synaptic transmission | Immunotherapy: 1. GCS together with steroid-sparing agents, IVIG, PE/IA, 2. rituximab, cyclophosphamide; Tumor-therapy: (operation, radiation, chemotherapy) | Complete remission upon tumor removal              | [10]                                           |
| Entity                        | Patients | Triggers | Clinical hallmarks                                                                 | Imaging                                      | Electrophysiology                                                                 | Laboratory                                                                 |
|-------------------------------|----------|----------|-----------------------------------------------------------------------------------|----------------------------------------------|-----------------------------------------------------------------------------------|-----------------------------------------------------------------------------|
| Anti-NMDA-R encephalitis      | Age 1–80 years (median 20 years), gender female 80, ANPR 500 | Tumors (age-, gender-, race-dependent, about 50 %; ovary/testis (teratoma), breast, lung (SCLC), lymphoma) | Multistage cortico-subcortical encephalopathy: 1. Prodromal phase (days) often with (viral) infections, 2. Psychiatric symptoms (1–2 weeks): psychosis, confusion, amnesia, dysphasia, 3. neurological symptoms (weeks): movement disorders (choreoathetoid, mute, catatonic), autonomic instability, respiratory failure, reduced consciousness, seizures, 4. recovery of symptoms in reverse of their appearance | MRI: no correlating signal abnormalities (50 %), transient T2/FLAIR hyperintense signal in cerebral cortex cerebellar cortex, basal ganglia, brainstem, spinal cord, Gd-enhancement in cortical meninges, basal ganglia, frontotemporal or mediotemporal cortical atrophy (50 %) | EEG: 1. focal or widespread interictal and ictal epileptiform activity, 2. generalized slowing, MRI: no correlating signal abnormalities (50 %), transient T2/FLAIR hyperintense signal in cerebral cortex cerebellar cortex, basal ganglia, brainstem, spinal cord, Gd-enhancement in cortical meninges, basal ganglia, frontotemporal or mediotemporal cortical atrophy (50 %) | Anti-NMDA-R (NR1/NR2) IgG1/3-antibody in serum and CSF, intrathecal anti-NMDA-R IgG1/3 synthesis, titers correlate well with clinical disease course/therapy tumors often express NMDA-R |
| Anti-AMPA-R encephalitis      | Age 40–80 years (median 60 years), gender female 90 %, ANPR 15 | Tumors (about 70 %); thymus (thymoma), breast, lung (SCLC, non-SCLC) | Limbic encephalitis: 1. focal temporal lobe and secondary generalized seizures, 2. short-term memory loss/ disorientation, 3. psychiatric symptoms (psychosis) evolving within days–weeks | MRI: T2/FLAIR hyperintense signal in one or both medial temporal lobes (often asymmetric), rarely Gd-enhancement (90 %) | EEG: 1. focal interictal and ictal epileptiform activity in one or both temporal lobes, 2. focal or generalized slowing | Anti-AMPA-R (Glur1/2) IgG antibody in serum and CSF, intrathecal anti-AMPA-R IgG1 antibody in serum and CSF, intrathecal anti-AMPA-R IgG synthesis, titers correlate with clinical disease course/therapy tumors often express AMPA-R |
| Anti-GABAγ-R encephalitis     | Age 25–75 years (median 60 years), gender female 50 %, ANPR 25 | Tumors (about 60 %): lung (SCLC, non-SCLC), thymus (thymoma) | Limbic encephalitis with prominent seizures: 1. focal temporal lobe and secondary generalized seizures, 2. short-term memory loss/ disorientation, 3. psychiatric symptoms (psychosis) evolving within days–weeks | MRI: T2/FLAIR hyperintense signal in one or both medial temporal lobes (often asymmetric), rarely Gd-enhancement (70 %) | EEG: 1. focal interictal and ictal epileptiform activity in one or both temporal lobes, 2. focal or generalized slowing | Anti-GABAγ-R (GABAγ) IgG1 antibody in serum and CSF, intrathecal anti-GABAγ-R IgG1 antibody in serum and CSF, intrathecal anti-GABAγ-R IgG synthesis, correlation of titers with clinical disease course/therapy not yet determined expression of GABAγ-R by tumors not yet determined |
| Anti-Glycine-R encephalitis   | Age 30–60 years (median 50 years), gender male 80 %, ANPR 4 | Tumors: typically none (thymoma) | Hyperekplexia, stiff-person syndrome, progressive encephalomyelitis with rigidity and myoclonus (PERM): stiffness/ rigidity, excessive startle, brainstem dysfunction | MRI: typically normal | EMG: excessive startle response, continuous involuntary motor activity | Anti-Gly-R (GlyRα1) IgG1 antibody in serum and CSF, intrathecal anti-Gly-R IgG1 antibody in serum and CSF, intrathecal anti-Gly-R IgG1 synthesis, titers seem to correlate with clinical disease course/therapy |
| Anti-VGKC complex encephalitis: LGI1 | Age 30–80 years (median 60 years), gender male 65 %, ANPR 120 | Tumors: (about 10 %): thymus (thymoma), lung (SCLC) | Limbic encephalitis: 1. focal temporal lobe and secondary generalized seizures, 2. short-term memory loss/ disorientation, 3. psychiatric symptoms (psychosis) evolving within days–weeks | MRI: T2/FLAIR hyperintense signal in one or both medial temporal lobes (often asymmetric), rarely Gd-enhancement | EEG: 1. interictal focal epileptiform activity or slowing over one or both temporal lobes, 2. ictal focal or generalized epileptiform activity | Anti-LGI1 IgG4/1 antibody in serum and CSF, intrathecal anti-LGI1 IgG4/1 antibody in serum and CSF, intrathecal anti-LGI1 IgG4/1 synthesis infrequent, correlation of titers with clinical disease course/therapy not yet determined expression of LGI1 by tumors not yet determined |
| Anti-VGKC complex encephalitis: CASPR2 | Age 45–80 years (median 60 years), gender male 85 %, ANPR 40 | Tumors: (about 10 %): thymus (thymoma), lung (SCLC) | Morvan’s syndrome: 1. psychiatric disturbance 2. seizures, 3. sleep disturbance (insomnia), 4. dysautonomia, 5. neuromyotonia in various combinations cerebellar | MRI: T2/FLAIR hyperintense signal in one or both medial temporal lobes (often asymmetric), rarely Gd-enhancement (about 40 %) | EEG: 1. focal or generalized interictal and ictal epileptiform activity, 2. focal or generalized slowing EMG: spontaneous doublet, triplet or multiplet single-unit discharges | Anti-CASPR2 IgG4/1 antibody in serum and CSF, intrathecal anti-CASPR2 IgG4/1 antibody in serum and CSF, intrathecal anti-CASPR2 IgG4/1 synthesis not determined, correlation of titers with clinical disease course/therapy or not yet determined expression of CASPR2 by tumors not yet determined |

**Table 2** Encephalitis associated with antibodies against neuronal surface membrane antigens (modified and extended from Melzer et al. [70])
Table 2 continued

| Entity                  | Patients | Triggers                          | Clinical hallmarks                      | Imaging                          | Electrophysiology                          | Laboratory | References |
|-------------------------|----------|-----------------------------------|----------------------------------------|----------------------------------|--------------------------------------------|------------|------------|
| Anti-mGlu-R1 encephalitis | Age 20–50 years, gender female 100 %, ANPR 3 | Tumors: none or Hodgkin lymphoma (in remission) | Cerebellitis                          | MRI: normal or T2/FLAIR hyperintense signal and atrophy of the cerebellum | –             | Anti-mGlu-R1 IgG antibody in serum and CSF, intrathecal anti-mGlu-R1 IgG synthesis, correlation of titers with clinical disease course/therapy not yet determined |
| Anti-mGlu-R5 encephalitis | Age 15–45 years, gender female 50 %, ANPR 2 | Tumors: Hodgkin lymphoma               | Limbic encephalitis (Opheilia syndrome): 1. focal temporal lobe and secondary generalized seizures, 2. short-term memory loss/dissociation, 3. psychiatric symptoms (psychosis) evolving within days–weeks | MRI: normal or T2/FLAIR hyperintense signal in one or both cortical and subcortical gray matter areas | EEG: 1. interictal focal epileptiform activity or slowing over one or both temporal lobes, 2. ictal focal or generalized epileptiform activity | Anti-mGlu-R5 IgG antibody in serum and CSF, intrathecal anti-mGlu-R5 IgG synthesis not determined, correlation of titers with clinical disease course/therapy not yet determined |
| Anti-P/Q type/N-type VGCC encephalitis | Age 30–80 years, gender male 80 %, ANPR 120 | Tumors: (about 50 %) lung (SCLC), breast, ovary | Cerebellitis, Lambert–Eaton myasthenic syndrome (LEMS) | MRI: normal or T2/FLAIR hyperintense signal and atrophy of the cerebellum | EMG: decrement of compound muscle action potential on 2–5/s repetitive nerve stimulation, increment of compound muscle action potential on 30–50/s repetitive nerve stimulation or “post-tetanic” stimulation | Anti-P/Q type/N-type VGCC IgG antibody in serum and CSF, intrathecal anti-P/Q type/N-type VGCC IgG synthesis, correlation of titers with clinical disease course/therapy not yet determined |
| Anti-nAch-R encephalitis | Age 17–103 years (median 65 years), gender male (55 %), ANPR 150 | Tumors (carcinoma in about 30 %): lung (non-SCLC, SCLC), breast, ovary, uterus, prostate, colon, thyroid, kidney, bladder (thymoma), melanoma | Cortical encephalitis, basal ganglionitis, dysautonomia peripheral (sensory, motor, sensorimotor, autonomic) neuropathy | MRI: usually normal, occasionally T2/FLAIR hyperintense signal in basal ganglia | EEG: generalized slowing Nerve conduction studies: predominantly axonal sensory, motor or sensorimotor neuropathy | Anti-nAch-R IgG antibody in serum and CSF, intrathecal anti-nAch-R IgG synthesis not yet determined, strong correlation of titers with clinical disease course/therapy expression of nAch-R by tumors not yet determined |

| Entity                | Patients | CSF | Neuropathology                  | Putative disease mechanisms | Therapy | Disease course and prognosis | References |
|-----------------------|----------|-----|---------------------------------|-----------------------------|---------|-----------------------------|------------|
| Anti-NMDA-R encephalitis | Age 1–80 years (median 20 years), gender female 80, ANPR 500 | Lymphocytic pleocytosis (median 32/µl, range 5–489/µl), normal glucose and lactate, mildly elevated protein (median 67 mg/dl, range 49–213 mg/dl), intrathecal IgG synthesis and OCB | Microglia activation, perivascular R cell/ plasma cell infiltrates, rare T cell infiltrates | Reversible IgG1/3-antibody-mediated NMDA-R crosslinking and internalization, alteration in glutamatergic synaptic transmission and plasticity, no neuronal cell death | Immunotherapy: 1. GCS together with steroids–sparring agents, IVIG, PE/IA, 2. rituximab, cyclophosphamide; tumor therapy; (operation, radiation, chemotherapy) | Monophasic or relapsing-remitting disease course; prolonged recovery over weeks–months (incomplete, spontaneous remission, accelerated and more complete remission under immunotherapy/tumor removal), frequent relapses (about 25 %) in patients without tumor or with insufficient immunotherapy | [15, 18, 20, 44, 47, 72, 100] |
| Anti-AMPA-R encephalitis | Age 40–80 years (median 60 years), gender female 90 %, ANPR 15 | Lymphocytic pleocytosis (median 24/µl, range 6–755/µl), normal glucose and lactate, normal–mildly elevated protein (median 51 mg/dl, range <46–420 mg/dl), intrathecal IgG synthesis and OCB | – | Reversible IgG-antibody-mediated AMPA-R crosslinking and internalization, alteration in glutamatergic synaptic transmission and plasticity, no neuronal cell death | Immunotherapy: 1. GCS together with steroids–sparring agents, IVIG, PE/IA, 2. rituximab, cyclophosphamide; Tumor therapy: (operation, radiation, chemotherapy) | Monophasic or relapsing-remitting disease course; good response to immunotherapy/tumor removal, frequent relapses (about 50 %) in patients without tumor or with insufficient immunotherapy | [32, 50, 72] |
| Entity Patients | CSF | Neuropathology | Putative disease mechanisms | Therapy | Disease course and prognosis | References |
|-----------------|-----|----------------|-----------------------------|---------|------------------------------|------------|
| Anti-GABAB-R encephalitis Age 25–75 years (median 60 years), gender female 50 %, ANPR 25 | Lymphocytic pleocytosis (median 200 µL, range 0–950 µL), normal glucose and lactate, normal-mildly elevated protein (median 35 mg/dL, range 22–109 mg/dL), intrathecal IgG synthesis and OCB | -- | IgG1-antibody-mediated GABAB-R blockade without internalization, alteration in GABAergic synaptic transmission and plasticity, impairment of pre- and postsynaptic GABAergic inhibition, no neuronal cell death | Immunotherapy: 1. GCS together with steroid-sparing agents, IVIG, PE/IA, 2. rituximab, cyclophosphamide; Tumor therapy: (operation, radiation, chemotherapy) | Monophasic or chronic disease course: good response to immunotherapy/tumor removal, rare relapses | [7, 53, 72] |
| Anti-Glycine-R encephalitis Age 30–60 years (median 50 years), gender male 80 %, ANPR 4 | CSF normal or lymphocytic pleocytosis (median 33 µL, range 0–60 µL), normal glucose and lactate, normal protein, intrathecal IgG synthesis/OCB | -- | IgG1-antibody-mediated Gly-R blockade, alteration in glycinergic synaptic transmission and plasticity | Immunotherapy: 1. GCS together with AZT/MMF, IVIG, PE/IA, 2. rituximab, cyclophosphamide; (tumor therapy) | Monophasic or relapsing disease course: good response to immunotherapy, occasional relapses | [45, 64, 72] |
| Anti-VGKC complex encephalitis: LGI1 Age 30–80 years (median 60 years), gender male 65 %, ANPR 120 | CSF normal or lymphocytic pleocytosis, normal glucose and lactate, normal or mildly elevated protein (median 35 mg/dL range up to 44 mg/dL), intrathecal IgG synthesis/OCB | -- | IgG4/1-antibody mediated disruption of the presynaptic VGKC complex and altered synaptic transmission | Immunotherapy: 1. GCS together with AZT/MMF, IVIG, PE/IA, 2. rituximab, cyclophosphamide, (tumor therapy) | Monophasic or relapsing disease course: good response to immunotherapy, occasional relapses | [46, 51, 72] |
| Anti-VGKC complex encephalitis: CASPR2 Age 45–80 years (median 60 years), gender male 85 %, ANPR 40 | CSF normal or lymphocytic pleocytosis (median 3 µL, range 0–1.5 µL), normal glucose and lactate, normal or mildly elevated protein (median 35 mg/dL range up to 44 mg/dL), intrathecal IgG synthesis/OCB | -- | IgG4/1-antibody mediated disruption of the para/juxtanodal VGKC complex and altered neuronal excitability | Immunotherapy: 1. GCS together with AZT/MMF, IVIG, PE/IA, 2. rituximab, cyclophosphamide, (tumor therapy) | Monophasic or relapsing disease course: spontaneous remission, good response to immunotherapy, relapses may occur | [4, 46, 52, 72] |
| Anti-mGlu-R1 encephalitis Age 20–50 years, gender female 100 %, ANPR 3 | CSF normal or lymphocytic pleocytosis (range 28–190 µL), normal glucose and lactate, normal or mildly elevated protein (range 28–72 mg/dL), intrathecal IgG synthesis/OCB | Purkinje cell loss with amputation of the dendritic tree, astrogliosis, no inflammatory cell infiltrates | IgG-antibody binding to mGlu-R1 at the perisynaptic site of Purkinje cell dendritic spines, impairment of cerebellar synaptic plasticity and motor learning, Purkinje cell death | Immunotherapy: 1. GCS together with AZT/MMF, IVIG, PE/IA, 2. rituximab, cyclophosphamide; | Monophasic or chronic disease course: good response to immunotherapy | [13, 62, 88] |
| Anti-mGlu-R5 encephalitis Age 15–45 years, gender female 50 %, ANPR 2 | Lymphocytic pleocytosis (range 23–114 µL), normal glucose and lactate, normal or mildly elevated, protein (range 40–55 mg/dL), intrathecal IgG synthesis/OCB | -- | IgG-antibody binding to mGlu-R5 on hippocampal neurons, impairment of synaptic plasticity, learning and memory | Immunotherapy: GCS together with AZT/MMF, IVIG, PE/IA Tumor therapy | Monophasic or chronic disease course: good response to immunotherapy/tumor therapy | [11, 55] |
Table 2 continued

| Entity Patients | CF | CSF | Neuropathology | Putative disease mechanisms | Therapy | Disease course and prognosis | References |
|-----------------|----|-----|----------------|-----------------------------|---------|-------------------------------|------------|
| Anti-P/Q type/N-type VGCC encephalitis Age 30–80 years, gender male 80 %, ANPR 120 | CSF normal or lymphocytic pleocytosis, normal glucose and lactate, normal or mildly elevated protein, intrathecal IgG/OCB | Purkinje cell loss, cerebellar cortical gliosis, rare or no inflammatory infiltrates in the cerebellum | IgG-antibody binding to P/Q type/N-type VGCC on central and peripheral neurons, impairment of neurotransmitter release, neuronal cell death | Immunotherapy: 1. GCS together with steroid-sparing agents, IVIG, PE/A, 2. rituximab, cyclophosphamide; tumor therapy: (operation, radiation, chemotherapy) | Chronic disease course: limited response to immuno-therapy/tumor therapy | [27, 34, 56, 65] |
| Anti-nACh-R encephalitis Age 17–103 years (median 65 years), gender male (55 %), ANRP 150 | CSF normal or lymphocytic pleocytosis (range 10–100/µl), normal glucose and lactate, normal or mildly elevated protein (median, 63 mg/dl; range, 48–181 mg/dl), intrathecal IgG/OCB | – | IgG-antibody binding to nACh-R on central and peripheral neurons, impairment of synaptic transmission | Immunotherapy: 1. GCS together with steroid-sparing agents, IVIG, PE/A, 2. rituximab, cyclophosphamide, tumor therapy: (operation, radiation, chemotherapy) | Monophasic or chronic disease course: good response to immuno-therapy/tumor therapy | [3, 31, 66, 95] |

AMPA 2-amino-3-(5-methyl-3-oxo-1,2-oxazol-4-yl)propanoic acid, ANPR approximate number of patients reported, AZA azathioprine, CSF cerebrospinal fluid, EEG electroencephalography, EMG electromyography, FLAIR fluid attenuated inversion recovery, GABA γ-aminobutyric acid, GABARAP γ-aminobutyric acid receptor associated protein, GCS glucocorticosteroids, IA immunoadsorption, IVIG intravenous immunoglobulins, mGlu metabotropic glutamate receptor, MMF mycophenolate mofetil, nACh nicotinic acetylcholine, NMMA N-methyl-D-aspartate, OCB oligoclonal bands, PE plasma exchange, SIADH syndrome of inappropriate antidiuretic hormone secretion, SCLC small cell lung cancer, VGCC voltage-gated calcium channels, VGKC voltage-gated potassium channels

Conclusions

A growing number of immune-mediated CNS disorders of paraneoplastic and non-paraneoplastic autoimmune origin have recently emerged, in which neurons are the target of the IgG antibodies are capable of activating T cell-mediated autoimmune CNS disorders of distinct autoimmune and non-autoimmune origins may differ between the CNS and peripheral organs. Moreover, with the growing clinical awareness of the latest class-switch to IgG and rarely with IgA antibodies against neuronal surface membrane antigens [78]. This may differ between the CNS and peripheral organs. While the CNS may respond to B-cell activation, B-cell and T-cell-mediated autoimmunity to different neural plasma membrane antigens [11] and to different autoantibodies. These conflicting results suggest that different autoantibodies and autoantigenic targets may differ in their capacity to induce distinct autoimmune mechanisms.
both adaptive cellular and humoral immune responses. In autoimmune encephalitis associated with antibodies to neuronal surface membrane antigens, potentially reversible mechanisms of antibody-mediated impairment of synaptic transmission and neuronal excitability prevail. Hence, these disorders offer unique insight and provoke further investigation into the consequences of immune-mediated disruption of distinct neuronal signaling pathways within the living CNS.

In contrast, paraneoplastic autoimmune encephalitis associated with antibodies to intracellular neuronal antigens seems to be mediated by cytotoxic CD8\(^+\) T cells that cause functional and structural neuronal impairment in a way not specific for the respective antigen.

Acknowledgments Scientific and clinical work of the authors is associated with antibodies to intracellular neuronal antigens. Further investigations into the consequences of immune-mediated transmission and neuronal excitability prevail. Hence, these disorders offer unique insight and provoke further investigation into the consequences of immune-mediated disruption of distinct neuronal signaling pathways within the living CNS.

Conflicts of interest All authors declare no relevant conflicts of interest. N.M. has received honoraria for lecturing and travel expenses for attending meetings from Biogen Idec, GlaxoSmithKline, and Fresenius Medical Care. S.G.M. has received honoraria for lecturing and travel expenses for attending meetings and has received financial research support from Bayer, Biogen Idec, Sanofi-Aventis, Bayer Schering, Novo Nordisk, Merck Serono Novartis, and Teva. H.W. has received funding for travel and speaker honoraria from Bayer Schering Pharma, Biogen Idec/Elian Corporation, Sanofi-Aventis, Merck Serono, and Teva Pharmaceutical Industries Ltd.; has served as a consultant for Merck Serono, Medac, Inc., Sanofi-Aventis/Teva Pharmaceutical Industries Ltd., Biogen Idec, Bayer Schering Pharma, Novartis, and Novo Nordisk, and receives research support from Bayer Schering Pharma, Biogen Idec/Elian Corporation, Sanofi-Aventis, Merck Serono, and Novo Nordisk.

Open Access This article is distributed under the terms of the Creative Commons Attribution License which permits any use, distribution, and reproduction in any medium, provided the original author(s) and the source are credited.

References

1. Alamowitch S, Graus F, Uchuya M, Rene R, Bescansa E, Delattre JY (1997) Limbic encephalitis and small cell lung cancer. Clinical and immunological features. Brain 120( Pt 6):923–928
2. Antoine JC, Honnorat J, Camdessanche JP, Magistris M, Abisi L, Mosnier JF, Petiot P, Kopp N, Michel D (2001) Paraneoplastic anti-CV2 antibodies react with peripheral nerve and are associated with a mixed axonal and demyelinating peripheral neuropathy. Ann Neurol 49:214–221
3. Baker SK, Morrillo C, Vernino S (2009) Autoimmune autonomic ganglionopathy with late-onset encephalopathy. Auton Neurosci 146:29–32
4. Becker EB, Zuliani L, Pettingill R, Lang B, Waters P, Dulneva A, Sobott F, Wardle M, Graus F, Bataller L, Robertson NP, Vincent A (2012) Contactin-associated protein-2 antibodies in non-paraneoplastic cerebellar ataxia. J Neurol Neurosurg Psychiatry 83:437–440
5. Bernal F, Shams’ili S, Rojas I, Sanchez-Valle R, Saiz A, Dalmau J, Honnorat J, Sillevis Smitt P, Graus F (2003) Anti-Tr antibodies as markers of paraneoplastic cerebellar degeneration and Hodgkin’s disease. Neurology 60:230–234
6. Bien CG, Vincent A, Barnett MH, Becker AJ, Blumcke I, Graus F, Jellinger KA, Reuss DE, Ribalt A, Schlegel J, Sutton I, Lassmann H, Bauer J (2012) Immunopathology of autoantibody-associated encephalitides: clues for pathogenesis. Brain 135:1622–1638
7. Boronat A, Sabater L, Saiz A, Dalmau J, Graus F (2011) GABA(B) receptor antibodies in limbic encephalitis and anti-GAD-associated neurologic disorders. Neurology 76:795–800
8. Briani C, Vitaliani R, Grisold W, Honnorat J, Graus F, Antoine JC, Bertolini G, Giometto B (2011) Spectrum of paraneoplastic disease associated with lymphoma. Neurology 76:705–710
9. Bruyland K, Crols R, Humble RL, Appel B, De Deyn PP (2006) Probably anti-Tr associated paraneoplastic cerebellar degeneration as initial presentation of a squamous cell carcinoma of the lung. Clin Neurol Neurosurg 108:415–417
10. Butler MH, Hayashi A, Ohkoshi N, Villmann C, Becker CM, Feng G, De Camilli P, Solimena M (2000) Autoimmunity to gephyrin in stiff-man syndrome. Neuron 26:307–312
11. Carr I (1982) The Ophelia syndrome: memory loss in Hodgkin’s disease. Lancet 1:844–845
12. Chan KH, Vernino S, Lennox VA (2001) ANNA-3 anti-neuronal nuclear antibody: marker of lung cancer-related autoimmunity. Ann Neurol 50:301–311
13. Coesmans M, Smitt PA, Linden DJ, Shigemoto R, Hirano T, Yamakawa Y, van Alphen AM, Luo C, van der Geest JN, Kros JM, Gaillard CA, Frens MA, de Zeeuw CI (2003) Mechanisms underlying cerebellar motor deficits due to mGlur1-autोantibodies. Ann Neurol 53:325–336
14. Cross SA, Salomao DR, Parisi JE, Kryzer TJ, Bradley EA, Mines JA, Lam BL, Lennox VA (2003) Paraneoplastic autoimmune optic neuritis with retinitis defined by CRMP-5-IgG. Ann Neurol 54:38–50
15. Dalmau J, Gleichman AJ, Hughes EG, Rossi JE, Peng X, Lai M, Dessain SK, Rosenfeld MR, Balice-Gordon R, Lynch DR (2008) Anti-NMDA-receptor encephalitis: case series and analysis of the effects of antibodies. Lancet Neurol 7:1091–1098
16. Dalmau J, Graus F, Villarejo A, Posner JB, Blumenthal D, Thissen B, Saiz A, Meneses P, Rosenfeld MR (2004) Clinical analysis of anti-Ma2-associated encephalitis. Brain 127:1831–1844
17. Dalmau J, Gultekin SH, Voltz R, Hoard R, DesChamps T, Balmaceda C, Batchelor T, Gerstner E, Eichen J, Frennier J, Posner JB, Rosenfeld MR (1999) Ma1, a novel neuron- and testis-specific protein, is recognized by the serum of patients with paraneoplastic neurological disorders. Brain 122( Pt 1):27–39
18. Dalmau J, Lancaster E, Martinez-Hernandez E, Rosenfeld MR, Balice-Gordon R (2011) Clinical experience and laboratory investigations in patients with anti-NMDAR encephalitis. Lancet Neurol 10:63–74
19. Dalmau J, Rosenfeld MR (2008) Paraneoplastic syndromes of the CNS. Lancet Neurol 7:327–340
20. Dalmau J, Tuzun E, Wu HY, Masjuan J, Rossi JE, Voloschin A, Baehring JM, Shimazaki H, Koide R, King D, Mason W, Sansing LH, Dichter MA, Rosenfeld MR, Lynch DR (2007) Paraneoplastic anti-N-methyl-D-aspartate receptor encephalitis associated with ovarian teratoma. Ann Neurol 61:25–36
21. De Camilli P, Thomas A, Cofiell R, Folli F, Lichte B, Piccolo G, Meinck HM, Austoni M, Fassetta G, Bottazzo G et al (1993) The synaptic vesicle-associated protein amphiphysin is the 128-kD autoantigen of stiff-man syndrome with breast cancer. J Exp Med 178:2219–2223
22. de Graaff E, Maat P, Hulsenaar E, van den Berg P, van den Bent M, Dammers J, Lugtenburg PJ, Hoogenraad CC, Sillevis Springsi
54. Lancaster E, Martinez-Hernandez E, Dalmau J (2011) Encephalitis and antibodies to synaptic and neuronal cell surface proteins. Neurology 77:179–189
55. Lancaster E, Martinez-Hernandez E, Titulaer MJ, Boulou M, Weaver S, Antoine JC, Liebers E, Kornblum C, Bengt CF, Honnorat J, Wong S, Xu J, Contractor A, Balice-Gordon R, Dalmau J (2011) Antibodies to metabolotropic glutamate receptor 5 in the Ophelia syndrome. Neurology 77:1698–1701
56. Lennon VA, Kryzer TJ, Griesmann GE, O'Suilleabhain PE, Wintzbank AJ, Wopmann A, Miljanich GP, Lambert EH (1995) Calcium-channel antibodies in the Lambert–Eaton syndrome and other paraneoplastic syndromes. N Engl J Med 332:1467–1474
57. Levy LM, Levy-Reis I, Fujii M, Dalakas MC (2005) Brain gamma-aminobutyric acid changes in stiff-person syndrome. Arch Neurol 62:970–974
58. Lucchinetti CF, Kimmel DW, Lennon VA (1998) Paraneoplastic and oncolgic profiles of patients seropositive for type 1 antineuronal nuclear autoantibodies. Neurology 50:652–657
59. Luque FA, Ferrueux HM, Erzerger R, Rosenblum MK, Wray SH, Schold SC Jr, Glanzt MJ, Jaakel KA, Biran H, Lesser M et al (1991) Anti-Ri: an antibody associated with paraneoplastic oposolosus and breast cancer. Ann Neurol 29:241–251
60. Malter MP, Helmsaetter C, Urbach H, Vincent A, Bie CF (2010) Antibodies to glutamic acid decarboxylase define a form of limbic encephalitis. Ann Neurol 67:470–478
61. Manto MU, Latue MA, Agura M, Rogemond V, Pandolfo M, Honnorat J (2007) Effects of anti-glutamic acid decarboxylase antibodies associated with neurological diseases. Ann Neurol 61:544–551
62. Marignier R, Chenevier F, Rogemond V, Sillevis Smitt P, Renoux C, Cavillon G, Andrijas G, Vukusic S, Graus F, Honnorat J, Confareux C (2010) Metabotropic glutamate receptor type 1 autoantibody-associated cerebellitis: a primary autoimmune disease? Arch Neurol 67:627–630
63. Martinez-Hernandez E, Horvath J, Shiloah-Malawsky Y, Sangha N, Martinez-Lage M, Dalmau J (2011) Analysis of complement and plasma cells in the brain of patients with anti-NMDAR encephalitis. Neurology 77:589–593
64. Mas N, Saiz A, Leite MI, Waters P, Baron M, Castano D, Sabater L, Vincent A, Graus F, Honnorat J, Confareux C (2010) Metabotropic glutamate receptor type 1 autoantibody-associated cerebellitis: a primary autoimmune disease? Arch Neurol 67:627–630
65. Martinez-Hernandez E, Horvath J, Shiloah-Malawsky Y, Sangha N, Martinez-Lage M, Dalmau J (2011) Analysis of complement and plasma cells in the brain of patients with anti-NMDAR encephalitis. Neurology 77:589–593
66. McKeon A, Lachance DH, Fealey RD, Pittok SJ (2009) Ganglionic acetylcholine receptor autoantibody: onological, neurological, and serological accompaniments. Arch Neurol 66:735–741
67. McKeon A, Pittok SJ (2011) Paraneoplastic encephalomyelopathies: pathology and mechanisms. Acta Neuropathol 122:381–400
68. McKeon A, Tracy JA, Pittok SJ, Parisi JE, Klein CJ, Lennon VA (2011) Purkinje cell cytoplasmic autoantibody type 1 accompaniments: the cerebellum and beyond. Arch Neurol 68:1282–1289
69. Melzer N, Meuth SG, Wiendl H (2009) CDS + T cells and neuronal damage: direct and collateral mechanisms of cytotoxicity and impaired electrical excitability. FASEB J 23:3659–3673
70. Melzer N, Meuth SG, Wiendl H (2012) Neuron-directed autoimmunity in the central nervous system: entities, mechanisms, diagnostic clues, and therapeutic options. Curr Opin Neurol 25:341–348
71. Meuth SG, Herrmann AM, Simon OJ, Siffrin V, Melzer N, Bittner S, Meuth P, Langer HF, Hallermann S, Boldakowa N, Her J, Munsch T, Landgraf P, Aktas O, Heckmann M, Lessmann V, Budde T, Kiesier BC, Zipp F, Wiendl H (2009) Cytotoxic CD8 + T-cell neuron interactions: perforin-dependent electrical silencing precedes but is not causally linked to neuronal cell death. J Neurosci 29:15397–15409
72. Moscato EH, Jain A, Peng X, Hughes EG, Dalmau J, Balice-Gordon RJ (2010) Mechanisms underlying autoimmune synaptic encephalitis leading to disorders of memory, behavior and cognition: insights from molecular, cellular and synaptic studies. Eur J Neurosci 32:298–309
73. Pedemonte E, Mancardi G, Giunti D, Corcione A, Benvenuto F, Pistoia V, Uccelli A (2006) Mechanisms of the adaptive immune response inside the central nervous system during inflammatory and autoimmune diseases. Pharmacol Ther 111:555–566
74. Pittok SJ, Lennon VA (2008) Aquaporin-4 autoantibodies in a paraneoplastic context. Arch Neurol 65:629–632
75. Pittok SJ, Lucchinetti CF, Lennon VA (2003) Anti-neuronal nuclear autoantibody type 2: paraneoplastic accompaniments. Ann Neurol 53:580–587
76. Pittok SJ, Lucchinetti CF, Parisi JE, Benarroch EE, Mokri B, Stephan CL, Kim KK, Kilimann MW, Lennon VA (2005) Amphiphysin autoimmunity: paraneoplastic accompaniments. Ann Neurol 58:96–107
77. Pittok SJ, Yoshikawa H, Ahlskog JE, Tisch SF, Benarroch EE, Kryzer TJ, Lennon VA (2006) Glutamic acid decarboxylase autoimmunity with brainstem, extrapyramidal, and spinal cord dysfunction. Mayo Clin Proc 81:1207–1214
78. Pruss H, Holtje M, Maier N, Gomez A, Buchert R, Harms L, Ahnert-Hilger G, Schmitz D, Terborg C, Kopp U, Klingbeil C, Probst C, Kohler S, Schwab JM, Stoecker W, Dalmau J, Wandler GP (2012) IgA NMDA receptor antibodies are markers of synaptic immunity in slow cognitive impairment. Neurology 78:1743–1753
79. Psimaras D, Carpentier AF, Rossi C (2010) Cerebrospinal fluid study in paraneoplastic syndromes. J Neurol Neurosurg Psychiatry 81:43–52
80. Raju R, Rakovec G, Chen Z, Hoehn G, Semino-Mora C, Shi W, Olsen R, Dalakas MC (2006) Autoimmunity to GABA(B) receptor in limbic encephalitis with seizures: case series and characterisation of the autoimmune response. J Neurol Neurosurg Psychiatry 81:43–52
81. Rojas I, Graus F, Keime-Guibert F, Rene R, Delattre JY, Ramon JM, Dalmau J, Posner JB (2000) Long-term clinical outcome of anti-Ri: an antibody associated with paraneoplastic oposolosus and breast cancer. Ann Neurol 67:470–478
82. Rosenfeld MR, Eichen JG, Wade DF, Posner JB, Dalmau J (2010) Antibodies to glutamic acid decarboxylase define a form of limbic encephalitis. Ann Neurol 67:470–478
83. Sadeghian H, Vernino S (2010) Progress in the management of paraneoplastic neurological disorders. Ther Adv Neurol Disord 3:43–52
84. Saiz A, Blanco Y, Sabater L, Gonzalez F, Bataller L, Casamitjana R, Ramio-Torrenta L, Graus F (2008) Spectrum of neurological syndromes associated with glutamic acid decarboxylase antibodies: diagnostic clues for this association. Brain 131:2553–2563
85. Shams’ili S, Grefkens J, de Leeuw B, van den Bent M, Hooijkaas H, van der Holt B, Vecht C, Sillevis Smitt P (2003) Paraneoplastic cerebellar degeneration associated with antineuronal antibodies: analysis of 50 patients. Brain 126:1409–1418
86. Shrikant PA, Rao R, Li Q, Kesterson J, Eppolito C, Mischo A, Singhal P (2010) Regulating functional cell fates in CD8 T cells. Immunol Res 46:12–22
87. Sillevis Smitt P, Grefkens J, de Leeuw B, van den Bent M, van Putten W, Hooijkaas H, Vecht C (2002) Survival and outcome in 73 anti-Hu-positive patients with paraneoplastic encephalomyelitis/sensory neuropathy. J Neurol 249:745–753
88. Sillevis Smitt P, Kinoshita A, de Leeuw B, Moll W, Coesmans M, Jaarsma D, Henzen-Logmans S, Vecht C, de Zeeuw C, Sekiyama N, Nakanishi S, Shigemoto R (2000) Paraneoplastic cerebellar ataxia due to autoantibodies against a glutamate receptor. N Engl J Med 342:21–27
89. Solimena M, Folli F, Aparisi R, Pozza G, De Camilli P (1990) Autoantibodies to GABA-ergic neurons and pancreatic beta cells in stiff-man syndrome. N Engl J Med 322:1555–1560
90. Solimena M, Folli F, Denis-Donini S, Comi GC, Pozza G, De Camilli P, Vicari AM (1988) Autoantibodies to glutamic acid decarboxylase in a patient with stiff-man syndrome, epilepsy, and type I diabetes mellitus. N Engl J Med 318:1012–1020
91. Sommer C, Weishaupt A, Brinkhoff J, Biko L, Wessig C, Gold R, Toyka KV (2005) Paraneoplastic stiff-person syndrome: passive transfer to rats by means of IgG antibodies to amphipathin. Lancet 365:1406–1411
92. Tschernatsch M, Gross O, Kneifel N, Kaps M, Blaes F (2009) SOX-1 autoantibodies in patients with paraneoplastic neurological syndromes. Autoimmun Rev 8:549–551
93. Tuzun E, Zhou L, Baehring JM, Bannikov S, Rosenfeld MR, Dalmau J (2009) Evidence for antibody-mediated pathogenesis in anti-NMDAR encephalitis associated with ovarian teratoma. Acta Neuropathol 118:737–743
94. Vernino S, Lennon VA (2000) New Purkinje cell antibody (PCA-2): marker of lung cancer-related neurological autoimmunity. Ann Neurol 47:297–305
95. Vernino S, Low PA, Fealey RD, Stewart JD, Farrugia G, Lennon VA (2000) Autoantibodies to ganglionic acetylcholine receptors in autoimmune autonomic neuropathies. N Engl J Med 343:847–855
96. Vincent A (2010) Successful ‘passive transfer’ of paraneoplastic stiff person syndrome with antibodies to an intracellular antigen. Brain 133:3164–3165
97. Vincent A, Bien CG, Irani SR, Waters P (2011) Autoantibodies associated with diseases of the CNS: new developments and future challenges. Lancet Neurol 10:759–772
98. Voltz R, Gultekin SH, Rosenfeld MR, Gerstner E, Eichen J, Posner JB, Dalmau J (1999) A serologic marker of paraneoplastic limbic and brain-stem encephalitis in patients with testicular cancer. N Engl J Med 340:1788–1795
99. Yu Z, Kryzer TJ, Griesmann GE, Kim K, Benarroch EE, Lennon VA (2001) CRMP-5 neuronal autoantibody: marker of lung cancer and thymoma-related autoimmunity. Ann Neurol 49:146–154
100. Zhang Q, Tanaka K, Sun P, Nakata M, Yamamoto R, Sakimura K, Matsui M, Kato N (2012) Suppression of synaptic plasticity by cerebrospinal fluid from anti-NMDA receptor encephalitis patients. Neurobiol Dis 45:610–615