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REVIEW

Paraneoplastic encephalomyelopathies: pathology and mechanisms

Andrew McKeon · Sean J. Pittock

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Abstract The last three decades have seen major advances in the understanding of paraneoplastic and idiopathic autoimmune disorders affecting the central nervous system (CNS). Neural-specific autoantibodies and their target antigens have been discovered, immunopathology and neuroimaging patterns recognized and pathogenic mechanisms elucidated. Disorders accompanied by autoantibody markers of neural peptide-specific cytotoxic effector T cells [such as anti-neuronal nuclear antibody type 1 (ANNA-1, aka anti-Hu), Purkinje cell antibody type 1 (PCA-1, aka anti-Yo) and CRMP-5 IgG] are generally poorly responsive to immunotherapy. Disorders accompanied by neural plasma membrane-reactive autoantibodies [the effectors of synaptic disorders, which include antibodies targeting voltage-gated potassium channel (VGKC) complex proteins, NMDA and GABA-B receptors] generally respond well to early immunotherapy. Here we describe in detail the neuropathological findings and pathophysiology of paraneoplastic CNS disorders with reference to antigen-specific serology and neurological and oncological contexts.

A. McKeon · S. J. Pittock
Department of Laboratory Medicine and Pathology,
Mayo Clinic, College of Medicine,
Rochester, MN 55905, USA

A. McKeon · S. J. Pittock
Department of Neurology, Mayo Clinic, College of Medicine,
Rochester, MN 55905, USA

A. McKeon (✉)
200 First Street S.W., Rochester, MN 55905, USA
e-mail: mckeon.andrew@mayo.edu

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Introduction

Central nervous system (CNS) dysfunction sometimes reflects an effective immune response to a systemic cancer that has devastating neurological consequences. The neurological presentation is often the first clue to the existence, or limited recurrence, of a cancer. Paraneoplastic neurological disorders are initiated as peripheral immune responses directed against autoantigens expressed in tumors. Tumor immune surveillance usually ensures that neoplasia is confined to the primary organ and in most cases one or more regional lymph nodes in these patients. The oncoantigens that drive the immune response are normally restricted to the nervous system [41]. The neurological attack can affect the central, peripheral somatic or autonomic nervous systems. Presentations are commonly multifocal rather than "classical" syndromes. Cancer may remain unsuspected and undetectable both clinically and by conventional radiology for long intervals after neurological symptom onset.

The advent of the technique of immunofluorescence microscopy 50 years ago led to early discovery of the first neural-specific autoantibody in a paraneoplastic context. Wilkinson and Zeromski used substrates of guinea pig, chick or human brain to discover what is now known as the type 1 anti-neuronal nuclear autoantibody (ANNA-1, or "anti-Hu") in serum of patients with subacute sensory neuronopathy occurring in the setting of lung carcinoma [172]. The Mayo Clinic Neuroimmunology Laboratory employs today a continuously optimized indirect immunofluorescence method, with a

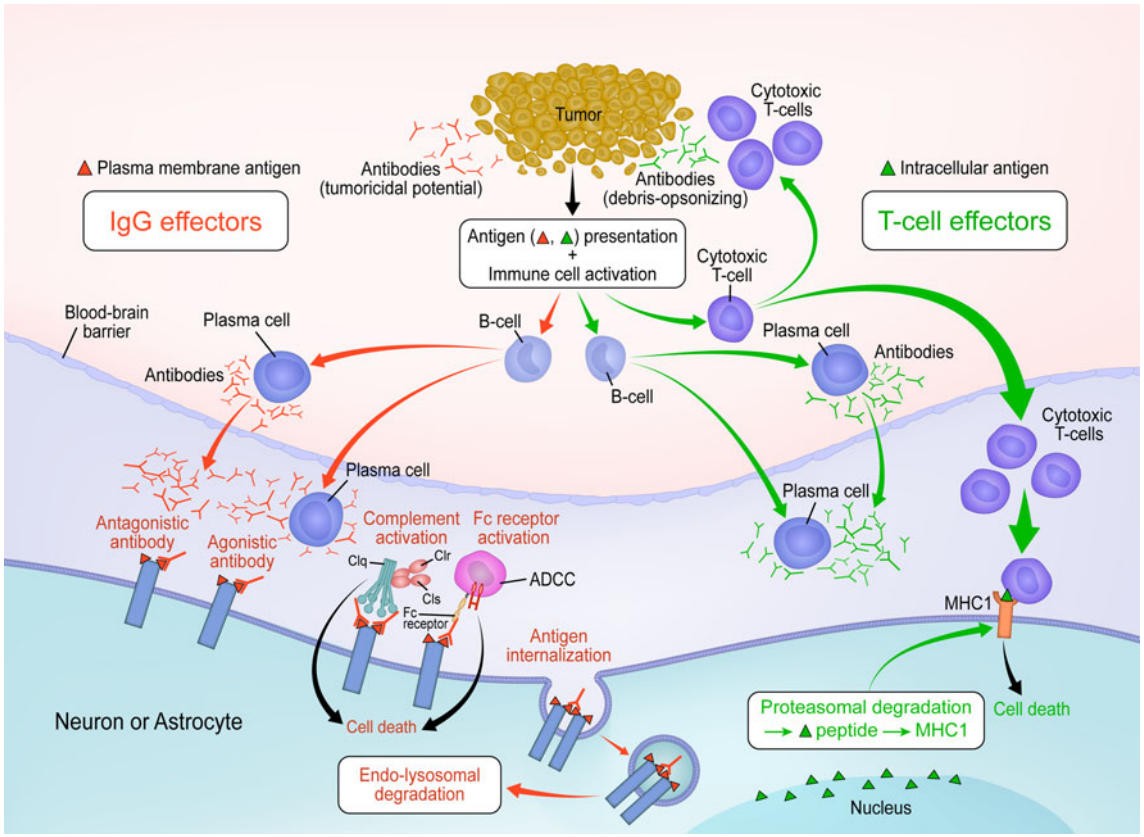

Fig. 1 Paraneoplastic neural autoantibodies and immunopathogenic mechanisms. Tumor-targeted immune responses are initiated by onconeural proteins expressed in the plasma membrane (*red triangle*) or in the nucleus cytoplasm or nucleolus (*green triangle*) of certain tumors. These antigens are presented to the adaptive immune system and immune cell activation results. These antigens are also expressed in neural cells (neurons or glia) and thus are coincidental targets. Antibodies targeting plasma membrane antigens are effectors of injury (*red*): antibodies (*red*) directed at neural cell plasma membrane antigens (e.g., VGKC complex, NMDA, AMPA, GABA-B receptor, aquaporin-4) are effectors of cellular dysfunction or injury through multiple effector mechanisms. These mechanisms include receptor agonist or antagonist effects, activation of the complement cascades, activation of Fc receptors [leading to antibody-dependent cell-mediated cytotoxicity (ADCC)], and antigen internalization (antigenic modulation), thereby altering antigen density on the cell surface. Antibodies targeting nuclear or cytoplasmic antigens are serum markers of a T cell effector mediated injury (*green*): intracellular antigens (*green triangles*) are not accessible to immune attack in situ, but peptides derived from intracellular proteins are displayed on upregulated MHC class-I molecules in a pro-inflammatory cytokine milieu after proteasomal degradation, and are then accessible to peptide-specific cytotoxic T cells. Antibodies (*green* e.g., ANNA-1, PCA-1) targeting these intracellular antigens (*green*) are detected in both serum and CSF but are not pathogenic. In clinical practice, these antibodies serve as diagnostic markers of a T cell-predominant effector process. Modified with permission (Nature Publishing Group) from Fig. 1 (antibodies can have a range of effector functions) from Diamond et al. Losing your nerves? Maybe it's the antibodies. Nature Reviews Immunology 2009; 9:449–456

composite substrate of rodent tissues, as an integral component of laboratory diagnostic screening for paraneoplastic autoantibodies. This technique also serves as a key discovery tool [3, 39, 80, 82, 89, 176]. Molecular identification of the targeted antigens has expedited development of confirmatory and high-throughput tests for serum and CSF, which permit early diagnosis of cancer and reveal the molecular pathogenic mechanisms underlying the neurological disease.

Immunohistopathological analyses of autopsied (and biopsied) tissues and experimental studies suggest that paraneoplastic neurological disorders for which the antigens of marker IgGs are intracellular (nuclear, nucleolar or cytoplasmic) are caused by CD8+ cytotoxic T cells. Intracellular antigens are not accessible to immune attack in situ, but peptides derived from intracellular proteins are displayed on upregulated MHC class-I molecules and are then accessible to peptide-specific cytotoxic T cells. Antibodies targeting these intracellular antigens are detected in both serum and CSF but are not pathogenic (Fig. 1). In clinical practice, these antibodies serve as diagnostic markers of a T cell-predominant effector process. A prototypic example is cerebellar degeneration occurring in patients who are seropositive for Purkinje cell cytoplasmic antibody type 1 (PCA-1, sometimes called "anti-Yo") [8]. This autoantibody predicts with 90% certainty the presence of adenocarcinoma of ovary, uterus, fallopian tube, peritoneum or breast [107, 120]. The target antigen is

cytoplasmic [cerebellar degeneration-related protein 2 (CDR2)] and therefore inaccessible in intact cells to circulating antibody. The neurological deficit rarely improves with antibody-depleting or tumoricidal therapies (and only in mildly affected patients). Afflicted patients die more often from complications of the neurological disorder than from metastatic cancer [107]. On the other hand, IgGs targeting neural cell surface receptors and channels do have a pathogenic role in effecting paraneoplastic disorders affecting the CNS. When these are the predominant antibody, the response to antibody-depleting therapies is usually excellent. For example, patients with antibodies targeting the ionotropic glutamate receptor [NR1 subunit of *N*-methyl D-aspartate (NMDA receptors), often associated with ovarian teratoma] present clinically with a stereotypic encephalopathy [38] which generally improves (sometimes completely) with early teratoma removal and immunotherapy targeted at removing antibody and reducing its production [38].

The focus of this review is the pathophysiology and immunopathology of paraneoplastic disorders affecting the CNS. Because the neurological presentations are often multifocal, we will discuss peripheral nervous system disease where relevant.

Neurological and oncological contexts

Clinical suspicion for a paraneoplastic neurological disorder is raised when the onset is subacute, with rapid progression and not readily explained by more common disorders. Neurological symptoms generally precede the diagnosis of cancer. Systemic cancer symptoms are distinctly uncommon in these patients. Risk factors for diagnosis of a paraneoplastic neurological disorder include personal or family history of cancer or autoimmunity and a history of smoking. Detection of one or more paraneoplastic neural autoantibodies in serum or CSF strongly supports the clinical suspicion and directs the search for cancer. Seronegativity does not exclude a paraneoplastic diagnosis. Classical syndromic CNS disorders, such as limbic encephalitis [29], brainstem encephalitis [46], encephalomyelitis [75], opsoclonus-myoclonus [79] and cerebellar degeneration [21], are relatively infrequent as the initial presentation. Experience based on our laboratory's continuing clinical–serological correlative observations has revealed that rather than being purely "syndromic", paraneoplastic disorders often have a multifocal presentation and evolution, including a mixture of CNS and peripheral nervous system findings [123]. For example, cerebellar degeneration is widely appreciated as the neurological presentation in PCA-1-seropositive patients. In a recently reported large series, it accounted for 77% of presentations, but 23% of patients initially presented with other neurological disorders, and cerebellar ataxia did not develop at all in 11% of patients [107]. Also, anti-neuronal nuclear antibody type 1 (ANNA-1, also known as 'anti-Hu'), is often considered to be syndromically associated with sensory neuronopathy, but accounted for only 40% of seropositive Mayo Clinic patients [93]. Other forms of neuropathy may occur [mixed sensorimotor (41%) or autonomic (27%)] and central nervous system presentations may also occur [including cerebellar ataxia (10%), limbic encephalitis (10%) and myelopathy (3%)] [93].

In many instances, the autoantibody profile in serum or CSF predicts the cancer type(s). For example, PCA-1 seropositivity is detected almost exclusively in women (99%) and has a 90% positive predictive value for adenocarcinoma, Müllerian (usually ovarian) or breast, sometimes both [107, 120]. ANNA-1 is found almost exclusively in patients with pulmonary or extra-pulmonary small-cell carcinoma [54, 93] or neuroblastoma, in children [35], and rarely with thymoma [161]. If another type of cancer is found, occult small-cell carcinoma should still be suspected. For neural plasma membrane-reactive autoantibodies, the positive predictive value for cancer is lower. NMDA receptor antibody is highly specific for ovarian teratoma, and thus usually found in women, but the frequency of tumor detection is also dependent on age and ethnicity. Teratoma is found in 50% of seropositive women between the ages of 25 and 30, but is less frequently detected in children and teenagers [38]. Teratoma is more commonly found in black women than among women of other racial groups [38]. Our laboratory reported that VGKC complex autoantibodies detected incidentally by immunostaining characteristics predicted cancer (current or in the past) in 33% of patients [154]. Lower frequencies of cancer detection have been reported when more sensitive radioimmunoprecipitation assays are used to screen selectively for VGKC antibodies [81, 165]. Our higher estimate is also consistent with the generally high cancer rate among Mayo Clinic patients evaluated serologically in the Mayo Clinic Neuroimmunology Laboratory: 17% of patients in whom no paraneoplastic autoantibodies were detected had a history of cancer [108].

Coexistence of multiple paraneoplastic autoantibodies in the same patient informs the cancer diagnosis [123]. For example, seropositivity for amphiphysin IgG predicts either small-cell carcinoma or breast adenocarcinoma. Among 63 Mayo Clinic patients with amphiphysin antibody and a known history of cancer, 33 had small-cell lung carcinoma, and 27 of those patients had one or more coexisting neural-specific autoantibodies which also predicted that cancer (82%). In contrast, no coexisting autoantibody was detected among 30 amphiphysin-IgG-positive patients in whom breast adenocarcinoma or other cancer type was found [104]. Autoantibodies sometimes

Table 1 Neuronal nuclear, cytoplasmic and nucleolar antibodies

Antibody	Antigen	Oncological association	Neurological presentations
ANNA-1	ELAVL (Hu)	Small-cell carcinoma	Limbic encephalitis, brainstem encephalitis, autonomic neuropathies, sensory neuronopathy, other peripheral neuropathies
ANNA-2	NOVA 1, 2 (Ri)	Small-cell carcinoma, breast adenocarcinoma	Dementia, limbic encephalitis, brainstem encephalitis, myelopathy, peripheral neuropathy
ANNA-3	Unknown	Aerodigestive carcinomas	Brainstem encephalitis, limbic encephalitis, myelopathy, peripheral neuropathy
AGNA	SOX-1	Small-cell carcinoma	Neuropathy, Lambert–Eaton syndrome, limbic encephalitis
Ma1, Ma2	PNMA1, PNMA2 (Ma1, Ma2)	Testicular (Ma2); breast, colon, testicular (Ma1)	Limbic encephalitis, hypothalamic disorder, brainstem encephalitis
PCA-1	CDR2	Müllerian adenocarcinoma, breast adenocarcinoma	Cerebellar ataxia, brainstem encephalitis, myelopathy, radiculopathies, peripheral neuropathies
PCA-2	Unknown	Small-cell carcinoma	Limbic encephalitis, ataxia, brainstem encephalitis, Lambert–Eaton syndrome, peripheral and autonomic neuropathies
PCA-Tr	Unknown	Hodgkin lymphoma	Cerebellar ataxia
CRMP-5 IgG	CRMP-5	Small-cell carcinoma, thymoma	Subacute-onset dementia, personality change, aphasia, depression, chorea, ataxia, myelopathy, radiculopathy, neuropathy, Lambert–Eaton syndrome
Amphiphysin IgG	Amphiphysin	Small-cell carcinoma, breast adenocarcinoma	Limbic encephalitis, aphasia, other subacute-onset dementias, stiff-person phenomena, myelopathy, neuropathy
GAD65 antibody	GAD65	Thymoma; renal cell, breast or colon adenocarcinoma	Stiff-man syndrome, stiff-man phenomena, ataxia, seizures, limbic encephalitis, brainstem encephalitis, ophthalmoplegia, parkinsonism, myelopathy
ZIC4 antibody	ZIC4	Small-cell carcinoma	Cerebellar ataxia

are detected only in CSF when the serum is negative, and vice versa. The higher diagnostic yield of testing of both serum and CSF justifies testing both when there is a high index of clinical suspicion for a paraneoplastic neurological disorder [105]. Factors that influence the likelihood of antibody detection in serum or CSF include the anatomical site of IgG synthesis (systemic or intrathecal), and the presence of interfering non-organ-specific antibodies (e.g., anti-nuclear or anti-mitochondrial) which are common in serum of patients with cancer, but are much rarer in CSF [59].

Pathophysiology and neuropathology

For simplicity, the authors favor an antibody nomenclature that is descriptive either of the antibody's immunohistochemical staining characteristics (e.g., ANNA-1), or its antigenic target when known (e.g., CRMP-5 IgG). For the purposes of a coherent pathophysiological discussion, the remainder of this review is divided into two sections (Fig. 1; Tables 1, 2): (1) neuronal nuclear, nucleolar and cytoplasmic antibodies: antibodies (not pathogenic) that reflect a cytotoxic CD8+ T cell-mediated neural degeneration; and (2) antibodies targeting neural plasma membrane ion and water channels, receptors and synaptic proteins: antibodies with potential to be the organ-specific effectors of the neurological disorder by binding to antigens residing in a neural plasma membrane.

Neuronal nuclear, nucleolar and cytoplasmic antibodies

ANNA-1

ANNA-1 (also known as "anti-Hu") is a marker of paraneoplastic autoimmunity associated with small-cell carcinoma (usually of lung) [54, 93], and is found in 20% of patients with uncomplicated small-cell carcinoma. Peripheral nervous system presentations are most common [clinical findings include peripheral neuropathies (sensory, motor, sensorimotor), radiculopathies, plexopathies autonomic neuropathies and cranial neuropathies] [54, 93]. Encephalomyelopathic presentations are also common. Immunohistochemistry of patient serum binds to nuclei of all neurons throughout the central and peripheral nervous system [6] (Fig. 2d, e).

Patients with ANNA-1 have an immune response targeting a family of proteins known as Embryonic Lethal Abnormal Vision-Like (ELAVL) or Hu (primarily HuD) which are expressed in both neurons and small-cell carcinoma [26, 97]. These RNA-binding proteins are implicated in post-transcriptional regulation of RNA in neurons [40]. CD8+ T cells isolated from ANNA-1 seropositive patients have been shown to target HLA–HuD peptide tetramers

Table 2 Antibodies targeting neural plasma membrane ion and water channels, receptors and synaptic proteins

Antibody	Antigen	Oncological association	Neurological presentationyc
VGKC- complex antibody	LGI1, CASPR2	Small-cell lung carcinoma; thymoma; adenocarcinoma of breast, prostate	Limbic encephalitis, amnestic syndrome, executive dysfunction, personality change, disinhibition hypothalamic disorder, brainstem encephalitis, ataxia, extrapyramidal disorders, myoclonus, peripheral and autonomic neuropathy
NMDA receptor antibody	NR1	Ovarian teratoma	Anxiety, psychosis, seizures, amnestic syndrome, extrapyramidal disorders
AMPA receptor antibody	GluR1,2	Thymic tumors, lung carcinomas, breast carcinoma	Limbic encephalitis, nystagmus, seizures
GABA-B receptor antibody	GABA-B	Small-cell lung carcinoma, other neuroendocrine neoplasia	Limbic encephalitis, orolingual dyskinesias
P/Q and N-type calcium channel antibody	P/Q and N-type calcium channels	Small-cell carcinoma, breast or gynecological adenocarcinoma	Encephalopathies, myelopathies, neuropathies, Lambert–Eaton syndrome
Muscle AChR antibody	Muscle AChR	Thymoma, thymic carcinoma, lung carcinoma	Myasthenia gravis. Also sometimes observed in paraneoplastic CNS contexts
Neuronal ganglionic AChR antibody	Neuronal ganglionic AChR	Adenocarcinoma, thymoma, small-cell carcinoma	Dysautonomia, peripheral somatic neuropathies, encephalopathies
NMO-IgG	Aquaporin-4	Some reports of thymoma and other solid tumors	Relapsing optic neuritis, transverse myelitis, encephalopathies
Glycine receptor antibody	α1 subunit GlyR	One case of thymoma reported	Stiff-man syndrome and variants

[133]. In some patients the peptide-specific CD8+ T lymphocytes had typical cytotoxic properties, while in others limited cytotoxic potential and properties shared by CD4+ type 2 (Th2) helper cells ("type 2 CD8+ lymphocytes", with producing mainly IL-5 and IL-13 cytokines). The significance of these findings is unclear but it has been speculated that limited tumor surveillance may occur in patients with the 'type 2 profile', and that the profiles may reflect different phases of the disease course, with a vigorous cytotoxic T cell response early on, and the 'type 2' response occurring in the chronic phase of the illness.

It has been thought for many years that the CNS is an immune-privileged site, and thus the immune system is ignorant of neuronal proteins [51]. If that hypothesis were true, then neural proteins ectopically expressed in small-cell carcinomas should be highly immunogenic in all patients. Clinical and experimental evidence demonstrates that there is likely immune tolerance rather than ignorance of neural proteins. Only approximately 20% of patients with small-cell carcinoma are seropositive for ANNA-1, and even fewer develop a paraneoplastic neurological disorder [41]. Also, mice immunized with HuD have been shown to not develop neurological disorders, despite high titers of the antibody in serum and CSF [27]. Experiments in mice have demonstrated that there is likely immune tolerance to HuD [43]. HuD-specific CD8+ T cells have been shown to be part of the repertoire of normal resting mice, but were not expanded with HuD immunization. Neurological disease did not develop with adoptive transfer of HuD CD8+ cytotoxic T cells, while HuD-specific T cells could be readily activated in HuD null mice [43]. In contrast cytotoxic T cells specific for the ubiquitously expressed HuA were not detected, possibly reflecting early central tolerance in the thymus through clonal deletion. The mechanisms whereby ongoing peripheral tolerance to HuD is maintained, despite the presence of these specific cytotoxic T cells, are unknown.

Autopsy studies of ANNA-1 seropositive patients with paraneoplastic encephalomyelitis revealed inflammatory infiltrates, gliosis, microglial nodules and neuronophagia [36, 74]. Gross examinations were typically normal. Perivascular infiltrates were composed of both B and T cells, while T cells predominated in parenchymal infiltrates [36]. CD4+ T cells predominated in the perivascular regions and CD8+ cytotoxic T cells were pervasive in the interstitial spaces [74]. Consistent with these observations of a cytotoxic T cell-mediated process, T cells expressing TIA-1 (a component of cytotoxic granules) were observed in clusters around neurons, but a marker of antibody-mediated complement activation (C9neo) was absent [16].

ANNA-2

ANNA-2 IgG (also known as anti-Ri) is found in patients with small-cell lung carcinoma or breast carcinoma [95, 125, 127]. Unlike ANNA-1, on indirect immunofluorescence, ANNA-2 does not bind to peripheral nervous system elements [57, 125]. Characteristic central nervous system

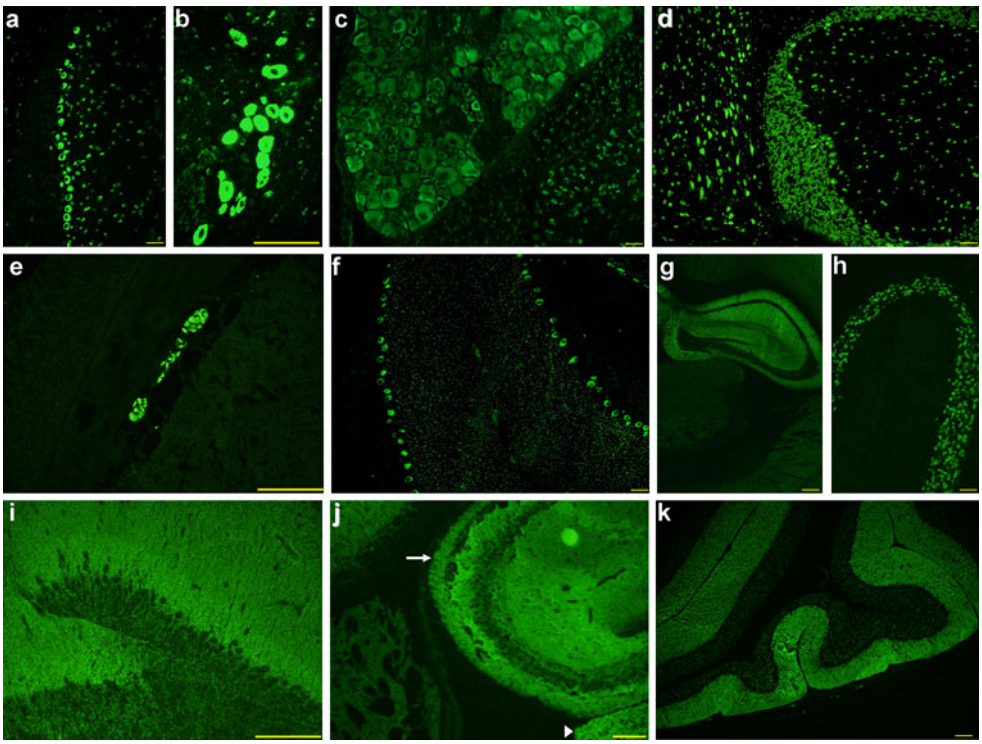

Fig. 2 Distribution of autoantibody immunoreactivity for PCA-1, ANNA-1, NMDA receptor antibody and GABA-B receptor antibody in mouse neural tissues. PCA-1 IgG binds to discrete cytoplasmic elements including Purkinje, molecular, and Golgi neurons in the cerebellar cortex (**a**), as well midbrain (**b**), cerebellar dentate, myenteric plexus and ganglionic neurons (not shown). Patient IgG also binds to spinal cord neurons, nerve root and dorsal root ganglion (**c**). ANNA-1 binds primarily to neuronal nuclei of cerebellar Purkinje, granular layer and molecular layer neurons (**d**, *right*), midbrain neurons (**d**, *left*) and myenteric plexus neurons (**e**). PCA-Tr stains Purkinje cell cytoplasm in a punctate pattern; distinctive small, bright puncta of staining are observed in the molecular layer (**f**). NMDA receptor antibody binds to neural synapses primarily in hippocampus (**g**, **i**) and cerebellar granular layer (**h**). GABA-B receptor antibody binds to neural synapses primarily located in hippocampus (**j**, *arrow*), thalamus (**j**, *arrow head*) and cerebellar molecular layer (**k**), while basal ganglia are negative (to the *left* of hippocampus in **h**). *Scale bars* represent 40 μm (**a**–**h**). Panels **a** and **b** reproduced with permission from the American Medical Association

disorders include cerebellar ataxia, myelopathy, and brainstem disorders (including jaw dystonia and laryngospasm).

ANNA-2 binds to two proteins (55 and 80 kDa), NOVA-1 and NOVA-2 [160, 174]. These highly conserved RNA-binding proteins are expressed in the adult nervous system and in small-cell carcinoma. NOVA-1 and 2 contribute to biodiversity through regulating alternative splicing of neuronal transcripts encoding synaptic proteins [136, 175], including Ca_V2 pre-mRNAs which encode subunits of N- and P/Q-type calcium channels [5], themselves targets of small-cell cancer-related autoimmunity [86]. Nova-2 deficiency has been shown to result in aberrant neuronal migration of cortical and Purkinje neurons; it is also thought that NOVA-2 (through regulation of the Reelin-DAB1 pathway) promotes migration of postmitotic neurons and lamination of the brain [175].

Autopsy studies of ANNA-2 seropositive patients who died after a protracted illness (and thus had chronic encephalomyelitis) demonstrated neuronal loss in the Purkinje cell layer, brainstem and spinal cord, with extensive gliosis [23, 66, 125, 127, 131, 164]. One detailed pathological study demonstrated perivascular lymphocytic infiltrates and a cellular infiltrate predominated by CD8+ T lymphocytes and CD68+ macrophages in the interstitium, with some CD20+ B cells and CD4+ T cells in the perivascular spaces, in addition to CD8+ cells (Fig. 3g, h) [127]. Pathological findings may be confined to specific spinal cord tracts or specific brainstem nuclei, correlating with neurological dysfunction. For example, two patients with gaze paresis both had pontine reticular formation involvement at autopsy [127].

ANNA-3

This is a rarely detected IgG autoantibody marker of small-cell lung carcinoma and adenocarcinoma (lung or esophagus) [28]. This antibody binds to a 170 kDa protein whose molecular identity remains to be elucidated. ANNA-3 has a distinctive immunofluorescence pattern, with antibody binding to Purkinje cell, Golgi, dentate and renal

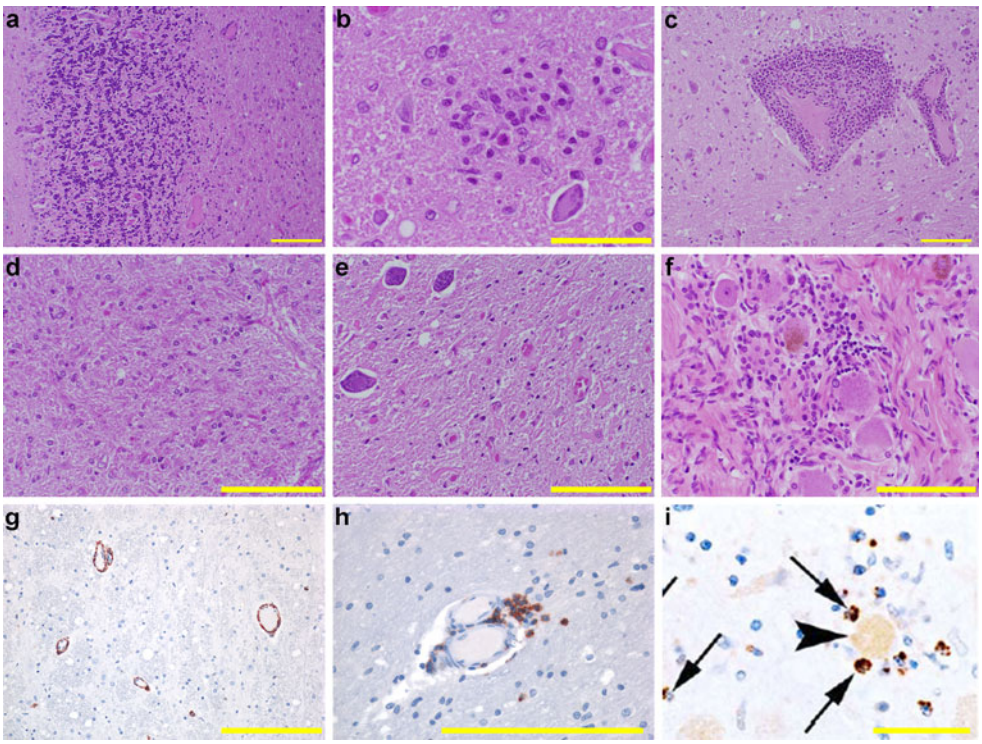

Fig. 3 Representative images from brain and spinal cord findings from autopsied cases with PCA-1 (**a**–**f**) and ANNA-2 (**g**, **h**) and Ma2 (**i**) autoimmunity. In the cerebellum, Purkinje neurons are absent; WM gliosis is marked, and the GL is largely preserved (**a** hematoxylin–eosin stain). In the pons, neuronophagia in the pontine tegmentum can be seen (**b** hematoxylin–eosin stain). In the pons, gliosis and perivascular lymphocytic cuffs in the basis pontis can be seen (**c** hematoxylin–eosin stain). In the lower medulla, microglial activation and marked gliosis can be seen (**d** hematoxylin–eosin stain). In the thoracic cord, anterior horn neuronal loss and marked gliosis can be seen (**e** hematoxylin–eosin stain). In the L1 dorsal root ganglion, dense lymphocytic infiltrates can be seen (**f** hematoxylin–eosin stain). In the pontine tegmentum, perivascular leukocytes are present (**g** CD45 immunostain). In the pons, a perivascular focus of cytotoxic T lymphocytes are observed (**h** CD8 immunostain). Multiple cytotoxic T cells can be surrounding 2 neurons (**i** granzyme-B stain). *Scale bars* represent 250 μm (**a**–**i**). Reproduced with permission from the American Medical Association (**a**–**h**) and Springer (**i**)

glomerular podocyte nuclei. Neurological accompaniments, often multifocal, include limbic encephalitis, cerebellar ataxia, myelopathy and peripheral nervous system disorders.

AGNA (SOX1) IgG

Antiglial/neuronal nuclear antibody (AGNA) is an antibody detected in some patients with paraneoplastic neurological disorders associated with small-cell lung carcinoma. Initial double-labeling immunohistochemical studies demonstrated staining of non-neuronal nuclei in the Purkinje cell layer [58]. Further work screening sera using a cerebellar expression library resulted in the isolation of a clone identical to the human *SOX1* [sex determining region Y (SRY)-box 1] gene [138]. Reports of neurological and oncological associations of AGNA have been largely confined to patients with Lambert–Eaton syndrome (LES) and small-cell lung carcinoma. Seropositivity for AGNA can aid the identification of patients with LES who are at the greatest risk for small-cell carcinoma [138]. Neurological dysfunction may also affect the limbic system, cerebellum, brainstem and peripheral nervous system [58, 158].

SOX1 belongs to a large family of transcription factors important for neurological development [4]. SOX proteins share a highly conserved 79 amino acid DNA-binding domain known as the High Mobility Group (HMG)-box. SOX1 and SOX2 are preferentially expressed in the Bergmann glia in the adult cerebellum, consistent with the immunoreactivity observed with AGNA. The human *SOX* gene family is classified in groups from A to H. *SOX1* belongs to group B1 along with *SOX2* and *SOX3*. *SOXB1* genes are strongly expressed in the developing nervous system and small-cell carcinoma cell lines [140], and their transcription is down-regulated (but not absent [4]) in adult brain.

No studies describing neuropathological findings in patients with AGNA have been published to date.

Ma1 and Ma2 antibodies

Antibodies targeting two antigens Ma1 and Ma2 [also known as paraneoplastic antigen (PNMA1) and PNMA2]

of molecular weight 40 and 42 kDa, respectively, have been described in association with paraneoplastic neurological disorders affecting primarily the mesial temporal lobes, diencephalon, brainstem and cerebellum [37, 135]. Patients seropositive exclusively for Ma2 antibodies, are usually men, have germ cell tumors of testis in 78% and have improved or resolved neurological symptoms with cancer treatment and immunotherapy [135]. Patients seropositive for Ma1 and Ma2, are more often women, have cancer types other than germ cell testicular tumors in 82% (including tumors of breast, colon, or ovary) and generally have a worse neurological outcome. Ma1 and Ma2 are expressed throughout the normal nervous system, and also in tumors; Ma1 is also expressed in normal testis. Immunofluorescence studies of patient serum for either Ma1 or Ma2 reveal neuronal-restricted staining of subcellular organelles including nucleoli [135].

The function of Ma proteins is unknown. Since Ma proteins do appear to be localized to nucleolus and other small structures, regions where ribonucleoproteins and ribosomal proteins are known to be concentrated, it has been speculated that they may play a role in RNA transcription [135]. Since there is homology between Ma proteins and an apoptosis-regulating protein, others have speculated that Ma proteins may be involved in apoptosis [143].

Consistent with Ma protein-specific antibodies not seeing these intracellular target antigens in vivo, and thus not being pathogenic, pathological and animal model studies have demonstrated that the neurological disorder is likely cytotoxic T cell mediated. Dalmau and colleagues reported two autopsy cases. Severe neuronal loss in the cerebellum and brainstem, Bergmann gliosis, brainstem inflammatory infiltrates (both parenchymal and perivascular) and microglial nodules were the most prominent findings [37]. Immunohistochemical analysis revealed that >90% of the cells were T lymphocytes, >75% of which were CD8+ cytotoxic T cells. Granzyme-B-positive cytotoxic T cells can be seen to surround neurons (Fig. 3i) [12]. These pathological findings (but not the neurological disorder) were recapitulated in a rat model into which T cells specific for autologous Ma1 were adoptively transferred [118]. Immunization with Ma1 protein resulted in Ma1 antibody production in the same model, but without pathological findings.

PCA-1

PCA-1 is detected in patients with paraneoplastic neurological disorders occurring in the setting of Müllerian or breast carcinoma. Indirect immunofluorescence studies of patient serum incubated with a composite of mouse tissues reveal neuronal cytoplasm-restricted staining [6] (Fig. 2a–c). Approximately 90% of patients develop cerebellar ataxia, frequently accompanied by brainstem, spinal cord or peripheral nervous system signs.

Molecular and immunological studies of specimens obtained from PCA-1 seropositive patients have been instructive for understanding the pathophysiology of inflammatory paraneoplastic neurological disorders mediated by CD8+ cytotoxic T lymphocytes [3, 31, 115]. The 52 kDa antigen identified by Western blot in CNS and cancer tissues, and encoded by a clone isolated from a cerebellar complementary DNA library, was identified as CDR2 [31] (which down-regulates DNA transcription through inhibition of c-Myc [115]). Emigration of expanded populations of MHC class I-restricted, CD8+ onconeural peptide-specific cytotoxic T lymphocytes from tumor-draining lymph nodes to the systemic circulation, and thence to the CNS, is a plausible mechanism for neuronal degeneration in patients with PCA-1 autoimmunity. Data from Albert et al. [3] support a neural peptide-specific T cell-mediated attack on neurons as the basis of irreversible neurological impairment in PCA-1-positive patients. It was demonstrated that antigen-specific cytotoxic T cells were activated in vitro by MHC-matched dendritic cells presenting CDR2 peptides to T cells isolated from seropositive patients.

Autopsied CNS tissue from PCA-1-seropositive patients reveal multifocal inflammatory changes, with perivascular and parenchymal CD8+ cytotoxic T lymphocytes throughout the cerebellum, brainstem, spinal cord and nerve rootlets (Fig. 3a–f) [107, 150]. In a study of two patients who during life had clinical signs of mixed cerebellar and pyramidal tract impairment, the distribution of PCA-1 immunoreactivity in mouse tissues paralleled the patients' clinical, radiological and pathological findings, including cells in the dorsal root ganglia and enteric nervous system and throughout the central nervous system (large neurons, hippocampus and brainstem) and in Schwann cells of the peripheral nervous system [107]. Gross and microscopic examinations of the cerebral hemispheres were normal in both patients. In these patients, the cerebellum, brainstem, spinal cord (at all levels) and dorsal root ganglia exhibited widespread perivascular inflammation, microglial activation, microglial nodules, patchy neuronal loss and gliosis. Immunophenotyping of lymphocytes revealed a predominance of perivascular and parenchymal CD8+ T cells. A study which included high magnification of cytotoxic T lymphocytes revealed them surrounding neurons with granzyme-B-positive granules polarized towards the neuron [1].

PCA-2

This relatively uncommon paraneoplastic IgG is associated with neurological disorders (cerebellar ataxia, encephalopathy, Lambert–Eaton myasthenic syndrome and

peripheral neuronopathy) occurring in the context of small-cell carcinoma [162]. The immunostaining pattern of PCA-2 in mouse tissues is distinct from that of the paraneoplastic autoantibodies PCA-1 and PCA-Tr. PCA-2 binds to cerebellar Purkinje somata and dendrites, neurons in internal granular layer and dentate nucleus, and neuronal elements in gut and kidney. Western blots of denatured cerebellar and SCLC proteins reveal a common antigenic band, of approximately 280 kDa, whose precise molecular identity is unknown.

PCA-Tr

In 1976, Trotter (hence the designation Tr) et al. described a 21-year-old woman with subacute-onset cerebellar ataxia and Hodgkin's lymphoma [157]. Using indirect immunofluorescence, the authors detected an antibody that stained Purkinje cell cytoplasm [157]. The molecular layer of cerebellum has also been noted to have a dotted staining pattern, suggesting possible immunoreactivity with dendrites (Fig. 2f) [55, 162]. The identity of the molecular target of PCA-Tr is unknown. Laser confocal microscopy and immunoelectron microscopy studies of rat brain confirmed prominent immunoreactivity in the cytosol and outer surface of the endoplasmic reticulum of the perikarya of molecular layer neurons and the cell body and dendrites of Purkinje cells without the involvement of dendritic spines [56]. Patients almost always present with a cerebellar disorder, and usually have Hodgkin disease [17], although PCA-Tr has also been reported in 7% of patients with paraneoplastic manifestations of non-Hodgkin lymphoma [22].

CRMP-5 IgG

Collapsin-response mediator-protein 5 (CRMP-5) IgG is detected as frequently as ANNA-1 in the Mayo Clinic Neuroimmunology Laboratory, and twice as often as PCA-1 [123]. It is a marker of small-cell carcinoma (77% of seropositive patients in 1 series) and thymoma (6% of seropositive patients in the same series) [176]. On indirect immunofluorescence, CRMP5-IgG has a characteristic synaptic pattern, with antibody binding to fixed sections of mouse cerebellar cortex, midbrain, and enteric plexus and nerves [176]. Common neurological manifestations include peripheral neuropathy, autonomic neuropathy, myelopathy [76] cerebellar ataxia, chorea ('basal ganglionitis'), optic neuritis (with or without retinitis) [32]. Distinct from CRMP-5 autoimmunity, antibody targeting CV2 is also detected in some patients with paraneoplastic neurological disorders [65].

CRMP-5 is the 62 kDa member of a family of nervous system-restricted proteins which mediate signaling by the axon repulsive guidance cue collapsin-1 (Sema3A) [142]. Their role in axon guidance may extend to mediation of cellular responses of a variety of other signals [8, 9].

Autopsy findings have been reported in one CRMP-5 IgG seropositive patient who had a multifocal disorder characterized by optic neuritis, retinitis, and encephalomyelopathy prior to death [32]. Examination of optic nerve demonstrated a CD8+ T cell-predominant infiltrate and corresponding areas of nerve fiber and myelin loss. Examination of the brain and spinal cord demonstrated microglial activation, rare microglial nodules and perivascular lymphocytic cuffing (90% CD8+ T cells) most prominent in mesial temporal structures, cerebellum, brainstem and spinal cord. Mild loss of myelinated axons was also noted in peripheral nerves, spinal rootlets and spinal sensory ganglia.

Amphiphysin antibody

De Camilli and colleagues [42] first reported an antibody targeting a 128 kDa antigen amphiphysin in the serum of three women who presented with a neurological disorder with predominant lower extremity stiffness associated with breast carcinoma. It was subsequently determined that breast carcinoma or small-cell carcinoma may be identified in seropositive patients [47]. Those patients with stiffness of the extremities and who are seropositive for amphiphysin antibody alone are more likely to be women with breast carcinoma [104, 126]. The neurological phenotype may be distinguished from the more classical stiff-man phenotype, where GAD65 antibodies are usually detected, and where paraneoplastic cases are exceptional [106, 110]. The neurological spectrum of presentations (often multifocal) is broader than stiffness alone, and includes encephalopathies, myelopathies, cerebellar disorders and neuropathies [126].

Amphiphysin is a presynaptic adaptor protein involved in synaptic vesicle endocytosis into the axon terminal after depolarization-induced exocytosis of neurotransmitter [91].

Neuropathological evaluation of autopsy specimens from amphiphysin-seropositive patients has revealed mild atrophy of cerebrum, brainstem and spinal cord. Microscopic abnormalities predominated in the brainstem and spinal cord, and included parenchymal and perivascular lymphocytes, with a CD8+ T cell-predominant infiltrate and CD68+ microglial cells, and B lymphocytes confined to perivascular regions [126, 170]. Leptomeninges were thickened and CD8+ lymphocytes were observed in these regions also [126]. Thus, the pathological findings pointed towards a cytotoxic T cell predominant-mediated pathogenesis of neurological dysfunction in amphiphysin antibody-seropositive patients. Contrary to this hypothesis, one group reported electrophysiology in an animal model

of amphiphysin autoimmunity and in vitro findings in mouse neuronal cell culture that the authors concluded represented evidence of a direct functional effect of amphiphysin antibody [52]. The authors reported that purified amphiphysin IgG injected intrathecally induced a stiff-man like disorder in rats. Muscle spasms, gait abnormalities, and evidence of reduced GABAergic spinal inhibition (reduced inhibition of the Hoffman spinal reflex) were reported in those rats but not in rats treated with control IgG. Furthermore, the authors reported internalization of fluorescent nanocrystal-tagged amphiphysin antibody into mouse hippocampal neurons and colocalization of IgG with presynaptic markers. The mechanisms by which IgG is purported to be endocytosed intact and then become a pathogenic effector have not been demonstrated.

GAD65 antibody

Glutamic acid decarboxylase (GAD) is an enzyme expressed both in the central nervous system and pancreatic islet cells that converts the excitatory neurotransmitter glutamate to the inhibitory neurotransmitter gamma-aminobutyric acid (GABA). The 65 kDa isoform of GAD has been identified as an autoreactive T cell target in autoimmune (type 1) diabetes mellitus [90]. Antibody targeting GAD65 is a sensitive and specific marker of type 1 diabetes [18]. GAD65 antibody is also often detected in patients with autoimmune neurological disorders in orders of magnitude higher than in patients with type 1 diabetes alone [148, 149]. Neurological presentations include painful spasms and stiffness primarily affecting the lumbar spine and lower extremity musculature (stiff-man syndrome) [109, 149], brainstem disorders, extrapyramidal disorders including cerebellar ataxia [128], epilepsy [119], peripheral somatic and autonomic nervous system disorders [45, 163]. Part of the continuum of stiff-man syndrome is a rapidly progressive encephalomyelopathy known as 'progressive encephalomyelitis with rigidity and myoclonus' (PERM) [171]; GAD65 antibody seropositive and seronegative forms have been described [10, 106]. GAD65 antibody-associated stiff-man syndrome occurs more commonly in an idiopathic context but paraneoplastic cases have also been reported (including breast, thyroid, colon and renal cell carcinoma) [2, 50, 100, 106]. GAD65 antibody is the most commonly detected neural antibody detected in patients with thymoma [163].

Since GAD65 is an intraneuronal antigen, GAD65 antibodies are unlikely to be pathogenic but may occur in the context of a T cell-mediated pathogenesis. An absence of clinical improvement with antibody-depleting therapies in many patients also supports these observations [33, 106]. Furthermore, it has been suggested that GAD65-reactive CD4+ T cells can cause a stiff-man-like syndrome in an animal model of the disease [24]. One group reported mice with a monoclonal GAD65-specific CD4+ T cell population developed a lethal encephalomyelitis. These GAD65-specific T lymphocytes and microglia were found throughout the CNS. High-titer GAD65 autoantibodies were also generated by GAD65-specific B cells, and had no effect on disease course or severity in mice.

Findings in neuropathological studies of GAD65 Ab seropositive stiff-man syndrome patients have included perivascular lymphocytic cuffing [169], vacuolar degeneration of anterior horn cells [139] and neuronal loss in the spinal cord [64, 73, 168, 169]. One further report described a patient with a rapidly progressive course of stiff-man syndrome who had clonally expanded GAD65-specific T cells detected in the CSF [64]. The patient did not respond to GABAergic or immunological therapies, including plasma exchange, and died from respiratory failure. Autopsy revealed axonal swelling, chromatolysis and vacuolization of anterior horn cells of the spinal cord, microglial proliferation and infiltration of CD8+ cytotoxic T cells. No CD4+ T helper cells, B cells or complement deposition were detected.

ZIC4 antibody

A rare antibody targeting the zinc-finger protein 4 (ZIC4) has been described in patients with small-cell lung carcinoma-associated paraneoplastic neurological disorders. Seropositive patients usually have coexisting antibodies predictive of small-cell carcinoma (82% have ANNA-1 or CRMP-5 IgG) [11], and thus clinical utility of ZIC4 antibody is limited. In animal models, mutations of different *ZIC* genes result in cerebellar malformation, holoprosencephaly, spina bifida, and sensorimotor gait abnormalities. Mutant *Zic1* mice serve as models of Joubert's syndrome, an autosomal recessive disorder characterized by hindbrain and cerebellar malformation [113]. There is no neuropathological data reported for patients seropositive for ZIC4 antibody alone.

Antibodies targeting neural plasma membrane ion and water channels, receptors and synaptic proteins

IgGs targeting plasma membrane proteins mediating intercellular communication (synaptic autoimmunity) are recognized in paraneoplastic and idiopathic contexts (Fig. 1; Table 2). This was first hypothesized as the basis of the neuromuscular postsynaptic transmission defect in myasthenia gravis [146, 147] and was subsequently extended to plasma membrane receptors in the endocrine system, and the central and autonomic nervous systems [84]. These disorders generally respond favorably to antibody-depleting therapies. Immunofluorescence (tissue

based or cell based) and immunoprecipitation assays are used to detect these antibodies. Immunofluorescence diagnostic criteria have been established for most well characterized synaptic IgGs.

VGKC-complex antibodies

Voltage-gated potassium channels (VGKCs) of the nervous system are critical for the regulation of neuronal excitability, axonal conduction, and neurotransmitter release [13]. Autoantibodies targeting macromolecular complexes containing the α-dendrotoxin-sensitive subset of the Kv1 family of VGKCs are associated with heterogenous neurological disorders, most notably encephalitides (limbic encephalitis is both prototypic and common) and peripheral nervous system hyperexcitability disorders [53, 154, 155, 165]. VGKC complex antibodies are encountered in both an idiopathic and paraneoplastic context in adult and pediatric patients [44, 154]. The incidence of cancer detection in patients seropositive for antibodies targeting potassium channels is relatively low (20–30% of patients systematically evaluated in clinical practice-based studies [154]) and the types of cancer detected are diverse, and include small cell carcinoma, thymoma, thyroid carcinoma, neuroblastoma and adenocarcinoma (prostate and colon).

Recent evidence suggests that some of the autoantibodies identified in clinical radioimmunoassays target some of the neuronal proteins complexed with VGKC that co-immunoprecipitate with detergent-solubilized VGKCs. In addition to VGKCs, these complexes contain cell adhesion molecules [including contactin-associated protein 2 (CASPR2, encoded by *CNTNAP2*), membrane-associated guanylate kinases, cytoskeletal scaffold, disintegrin and metalloproteinase 22 (ADAM22), and a soluble binding partner of ADAM22, leucine-rich, glioma inactivated 1 (LGI1) protein] [112]. CASPR2 when complexed with contactin forms tight paranodal junctions between axons and glial cells [114]. CASPR2 also concentrates VGKCs at the juxtaparanodal region of myelin [129, 130]. The principal antigens identified in VGKC complex autoimmunity to date include: LGI1 in patients with limbic encephalitis, and CASPR2 in some patients with acquired neuromuscular hyperexcitability, steroid-responsive peripheral neuropathies, dysautonomias and encephalopathies [71, 72, 81]. CASPR2-reactive IgG has been reported in neurological patients with thymoma [71]. Clues to the importance of these two molecules in the regulation of CNS homeostasis included the recognition of LGI1 as an epilepsy-linked protein [144] and the occurrence of intractable partial seizures among Amish children with a homozygous mutation of *CNTNAP2* [151].

Neuropathological reports of VGKC complex antibody-seropositive patients included perivascular and parenchymal lymphocytes, astrogliosis, and diffuse microglial activation in biopsied or resected mesial temporal regions [48, 116, 165]. In two studies, perivascular T cell infiltrates were also noted [48, 116]. One detailed report described postmortem findings [77]. Pathologic changes were reported in both hippocampi and the right amygdala. There was loss of pyramidal neurons in the CA4 region and relative sparing of the CA3, 2, and 1 regions, associated with marked microglial activation and astrocytosis extending to the subiculum. The amygdala showed less prominent changes than that observed in the hippocampi. The remainder of the temporal lobes showed only mild reactive changes. Consistent with an antibody-mediated disorder, perivascular lymphocytic infiltrates predominantly of CD20+ B cells lineage were observed.

Antibodies targeting ligand-gated ionotropic glutamate receptors

NMDA receptor antibody

In 2005, a neurological disorder with a stereotyped clinical course was described in four young women with ovarian teratoma [167]. It was later determined that these patients had autoantibody yielding a hippocampus-predominant synaptic immunohistochemical staining pattern on mouse tissue (Fig. 2g, i). This autoantibody targets the NR1 (GluN1) subunit of the NMDA receptor [39], an ionotropic glutamate receptor [121]. This discovery has been of great importance to clinical practice since it identified a common, devastating (and potentially fatal) yet treatable neurological disorder. In one series, 1% of people aged 18–35 admitted to ICU with encephalitis of unknown cause were seropositive for NMDA receptor antibody [132]).

The evolving neuropsychiatric disorder usually has a characteristic pattern [70, 141]. About 70% of patients have prodromal flu-like symptoms followed within days by psychiatric symptoms (including psychosis) and short-term memory loss. Later on, abnormal movements, seizures, autonomic instability, hypoventilation requiring respiratory support and coma ensue [38]. Dissociative responses to stimuli similar to that seen with NMDA receptor antagonists such as phencyclidine are noted in some; for example, patients often resist eye opening but are unresponsive to painful stimuli [38]. NMDA receptors are critical for the regulation of synaptic plasticity and network synchronization in other neuropsychiatric disorders [14]. For example, NMDA receptor-mediated synaptogenesis may contribute to the pathophysiology of schizophrenia and Alzheimer disease.

Data from in vitro experiments are consistent with the hypothesis that NMDA receptor encephalitis is antibody mediated. Rat hippocampal neurons treated with patient

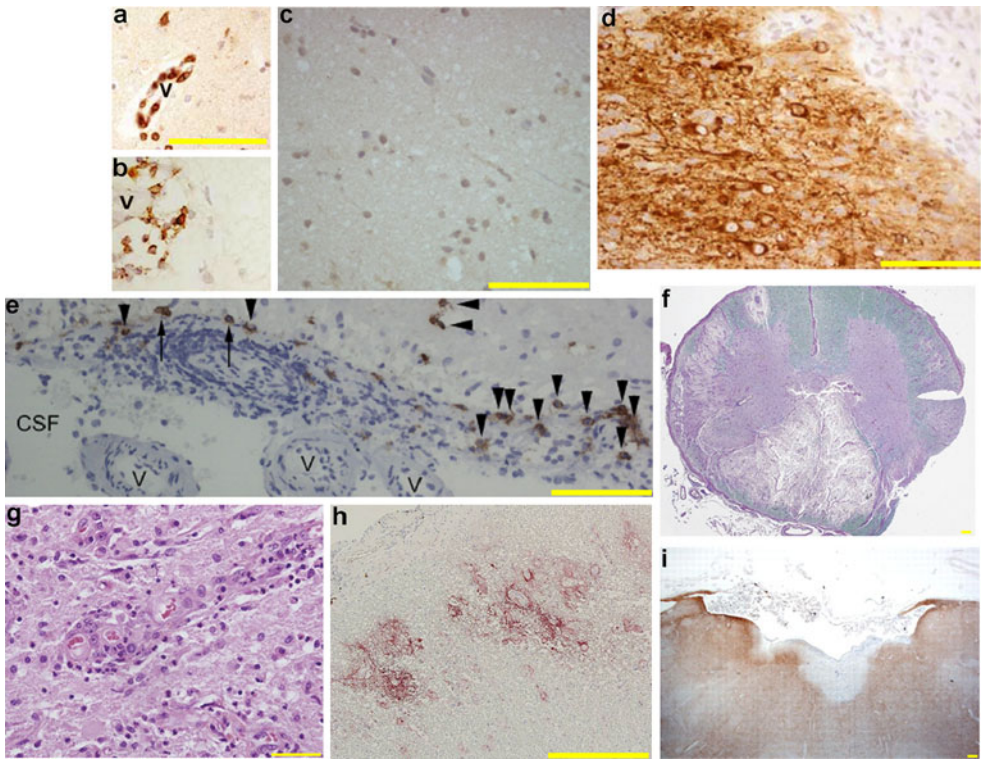

Fig. 4 Representative images of neuropathological findings for patients with NMDA receptor antibody encephalitis (**a**–**e**) and neuromyelitis optica (**f**–**i**). Perivascular (*v*) lymphocytic cuffing is dominated by CD20+ B cells (**a**) and CD79a+ plasma cells (**b**). C9neo staining (representing membrane attack complex components of complement) is absent in the brain (**c**), but is abundant in teratoma from the same patient (not shown). Abundant neurological tissue in teratoma is demonstrated by MAP-2 staining (**d**). In Virchow–Robin spaces (**e**) the CD138+ cells are in perivascular regions (*arrows*) and along the tissue surface (*arrow heads*) that delineates spaces containing CSF and small vessels (*v*). Extensive demyelination of the grey matter and white matter is observed at the level of the thoracic cord [**f** Luxol fast blue-periodic acid Schiff (LFB-PAS) stain for myelin]. The inflammatory infiltrate contains perivascular and parenchymal eosinophils and granulocytes (**g** hematoxylin and eosin stain). Prominent vasculocentric complement activation, in a characteristic rim and rosette pattern surrounding thickened blood vessels [**h** immunocytochemistry for C9neo antigen (*red*)]. Medullary floor of the fourth ventricle; aquaporin-4 loss (**i**) is observed in an inflammatory NMO focus lacking demyelination (not shown). *Scale bars* represent 250 μm (**a**–**i**). Reproduced with permission from Springer publishers (**a**, **b**, **d**), Lippincott, Williams and Wilkins (**c**, **e**), Elsevier (**f**–**h**) and Oxford University Press (**i**)

CSF or with NMDA receptor IgG isolated from serum have been demonstrated to have decreased surface NMDA receptor clusters which are reversible on removal of antibody [34, 38, 68]. This loss is proportional to the quantity of IgG present. Antigenic modulation (bivalent IgG antigenic crosslinking, followed by internalization) has been identified as a likely disease mechanism [68]. Although patient antibody can activate complement, in vitro deposits of complement have not been detected in patient brain tissue (Fig. 4c) [98, 159].

Some functional consequences of NMDA receptor autoimmunity have been reported. Patch clamp recordings showed that patients' antibodies specifically decreased synaptic NMDA receptor-mediated excitatory postsynaptic currents [68]. Neuropathological studies have demonstrated findings largely confined to the hippocampi and amygdala including loss of pyramidal neurons, rare neuronophagia, extensive gliosis and microglial proliferation [39]. Lymphocytic infiltrates were scattered in the leptomeninges and in a perivascular distribution, and to a lesser extent in brain parenchyma. Significant deposits of IgG were identified predominantly in the hippocampus. Extratemporal findings included rare pyramidal neuron loss and microglial proliferation in the medulla and spinal cord. Immunological findings in autopsied patients have been described in more detail in further work (Fig. 4a–e) [98, 159]. T cell infiltrates (mainly in the leptomeningeal and perivascular regions) and markers of cytotoxicity (such as granzyme-B and perforin) were scant in brain and spinal cord. B cells were predominantly found in the perivascular regions. Antibody secreting plasma cells were predominantly found in perivascular, interstitial, and Virchow–Robin spaces. IgG (predominantly IgG1 and 3 subtypes) deposits are seen throughout the CNS, but without complement deposition. In contrast, tumors showed positivity for both cytotoxic markers and complement. Infusion of

patient IgG into the hippocampi of female Lewis rats reduced NMDA receptor density, similar to that observed in patient autopsy hippocampal specimens [68].

Consistent with these experimental and neuropathological findings available to date, treatment of affected patients with antibody-depleting therapies and with removal of the antigenic source driving the immune response (teratoma) permits full or nearly full recovery in 75% of patients [38].

AMPA receptor antibody

α-Amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid receptors (AMPARs) are ionotropic glutamate receptors that are highly conserved among mammals and mediate most of the fast excitatory neurotransmission in the brain [111, 156]. Most AMPA receptors are tetramers composed of GluR (GluA) 1, 2, 3 or 4 subunits [156]. Antibodies targeting the extracellular domains of either or both of the GluR1 or GluR2 subunits of AMPA receptors have been reported in a group of ten patients with thymoma, breast carcinoma or lung carcinoma (small-cell or non-small cell)-associated limbic encephalitis [80]. AMPA receptor antibodies cause receptor crosslinking and internalization (antigenic modulation), resulting in a reversible decrease in AMPA receptor clusters at synapses [80].

Disruption of AMPA receptor function has been implicated in non-autoimmune neurological disorders. For example, mouse models of fragile X syndrome have demonstrated excessive internalization of AMPA receptors resulting in enhanced long-term depression in the hippocampus and impaired long-term potentiation in the amygdala [152, 153]. The regions with the greatest levels of GluR1/2 and GluR2/3 receptors are the synaptic CA3–CA1 areas of the hippocampus, the amygdala, cerebellum, caudate-putamen, and cerebral cortex, similar to the distribution of immunostaining of patient antibody [80].

Of the ten patients reported seropositive for AMPA receptor antibodies, three had coexisting neural autoantibodies detected: CRMP-5-IgG, 1; SOX1–IgG, 1; GAD65 antibody, 1. Antibody-depleting therapies brought about rapid improvements in patients, but relapses were frequent on discontinuation of immunotherapy. Neuropathological descriptions for two patients were also described [80]. Of note, a patient with a rapid neurological demise was a 44-year-old woman with thymoma who had coexisting CRMP-5 autoimmunity. This poor outcome may be explicable by an aggressive cytotoxic T cell-mediated disorder that occurred in addition to AMPA receptor autoimmunity. Neuropathological examination of autopsy materials from that patient revealed perivascular and interstitial inflammatory infiltrates, microglial proliferation, microglial nodules and astrocytosis that predominated in the hippocampi. The cellular parenchymal infiltrate was predominantly composed of CD8+ cytotoxic T cells [80]. Neuropathological data available for a 59-year-old woman with small-cell lung carcinoma, who died of myocardial infarction and had coexisting SOX-1 antibody and N-type calcium channel antibody contrasted with the patient seropositive for CRMP-5 IgG. Studies revealed mild perivascular lymphocytic cuffing and scattered foci of lymphocytes in the hippocampal parenchyma, predominantly in the CA4 region. Microglial nodules were rarely identified [80].

GABA-B receptor antibody

Antibody targeting extracellular domains of the B1 subunit of the GABA-B receptor has been reported in a group of patients with small-cell carcinoma-related autoimmune limbic encephalitis, usually with prominent seizures [82]. On mouse tissue immunofluorescence, a synaptic pattern of antibody staining predominates in hippocampus, thalamus and cerebellar molecular layer [82] (Fig. 2j, k).

The B1 subunit of GABA-B receptors is necessary for GABA binding and receptor function. GABA-B receptors are G-protein-coupled receptors composed of GABA-B1 and GABA-B2 subunits. GABA-B receptors mediate presynaptic and postsynaptic inhibition, through suppression of neurotransmitter release and prolonged neuronal hyperpolarization, respectively [67]. GABA-B receptor antibodies have been reported to block receptor function, but not cause receptor internalization [83].

In the initial report of 15 patients, one or more coexisting antibodies were documented in seven patients (N-type calcium channel antibody, 3; GAD65 antibody, 3; thyroid antibodies, 3; SOX-1 antibody, 1) [82]. One of the three patients with N-type calcium channel antibodies and the patient with SOX-1 antibody had small cell lung carcinoma. Consistent with the disease pathogenesis being mediated through the pathogenic effects of B1 subunit-specific antibody, patients who received antibody-depleting therapy had clinical improvements [82]. Since the GABA-B receptor agonist baclofen has therapeutic benefit in stiff-man syndrome, investigators evaluated GAD65 antibody-seropositive stiff-man patients for GABA-B antibody; none of 29 patients tested were seropositive [19]. However, 10 of 70 GAD65 antibody-positive patients with limbic encephalitis (14%) were GABA-B receptor antibody seropositive [19]. Neuropathology data of biopsy or autopsy specimens have not been published to date.

P/Q and N-type calcium channel antibodies

Antibodies targeting conotoxin-sensitive calcium channels are detected by immunoprecipitation assays in over 90% of patients with Lambert–Eaton syndrome [86], a myasthenic

disorder where the regulated influx of calcium through voltage-gated channels in the presynaptic terminal is disturbed, thus impairing acetylcholine release from synaptic vesicles in the nerve terminal [49]. These autoantibodies are also frequently detected in patients with paraneoplastic encephalomyelopathies, most commonly in the setting of small-cell lung carcinoma, and breast or ovarian adenocarcinomas [86].

Acetylcholine receptor antibodies

Myasthenia gravis and autoimmune dysautonomia are neurological disorders whose pathogenicities are attributed to muscle acetylcholine receptor antibody and neuronal ganglionic acetylcholine receptor antibody, respectively [85, 88]. Other paraneoplastic neurological disorders, including encephalopathies and myelopathies, have also been observed in seropositive patients [101, 102, 163].

NMO-IgG (aquaporin-4 IgG)

Advanced clinical and pathophysiological understanding of an autoimmune water channelopathy of the CNS has evolved over the last 7 years. The target autoantigen, aquaporin-4, is highly expressed in astrocytic end-feet in the blood–brain barrier, nodes of Ranvier and neuronal synapses [49, 61, 87, 89]. Although the factors that initiate autoimmunity targeting aquaporin-4 are unknown in most patients, it has been observed in some that the immune response is initiated against tumor antigens [124]. Neoplasms observed to date in the context of aquaporin-4 autoimmunity include thymoma, breast carcinoma, lung carcinoma, thyroid Hürthle cell, carcinoid, pituitary somatotropinoma, and B cell lymphoma [124]. The incidence of cancer overall among patients with NMO-IgG in that study was 5%, thus there are likely other as yet unknown environmental or genetic factors that trigger aquaporin-4 autoimmunity. The clinical disorders encountered are predominantly relapsing optic neuritis and myelitis (usually longitudinally extensive) [173] and a variety of encephalopathic presentations, most commonly seen among children [7, 92, 103].

In vitro studies have demonstrated that binding of NMO-IgG to astrocytic aquaporin-4 initiates multiple potentially pathogenic mechanisms. Downregulation of aquaporin-4 occurs through antigenic modulation (binding of bivalent IgG to adjacent aquaporin-4 molecules), followed by internalization of antigen from the plasma membrane, and targeting of antigen to lysosomes [62]. This occurs in tandem with downregulation of the glutamate transporter excitatory amino acid transporter 2 (EAAT-2, physically linked to aquaporin-4) resulting in disruption of water and glutamate homeostasis [63]. Also, binding of NMO-IgG (mainly IgG1 subclass) to aquaporin-4-expressing cells in the presence of complement, activates the classical complement cascade, leading to membrane lesioning [62, 63]. The inflammatory consequences for the blood–brain barrier have been demonstrated in a system combining co-cultured astrocytes, endothelial cells and leukocytes [166]. Addition of NMO patient serum to this system promotes migration of granulocytic leukocytes across the endothelial layer (in the presence of complement), natural killer cell migration (in the absence of complement) and increased permeability of the endothelial barrier to fluorescent serum albumin [166]. An IL-6-dependent B cell subpopulation of plasmablasts may be involved in the pathogenesis of NMO. Chihara [30] and colleagues recently demonstrated that the plasmablast population was expanded during NMO relapse, and that interleukin 6 (IL-6) enhanced their survival and their aquaporin-4 antibody secretion, whereas the blockade of IL-6 receptor reduced the survival of plasmablasts.

Pathological findings in neurological specimens evaluated at autopsy or biopsy from patients with NMO have paralleled the in vitro disease models, and are distinct from the neuropathology of multiple sclerosis (Fig. 4f–i). Demyelination and necrosis were reported in both white and grey matter, and blood vessels were thickened and hyalinized [94]. In active lesions, edema and leukocytic infiltrates were prominent, with mononuclear cells (lymphocytes, macrophages and plasma cells) and polymorphs (neutrophils and eosinophils) observed. Immune complexes (IgG, IgM and complement components) were deposited in a vasculocentric pattern [94]. Loss of aquaporin-4 and EAAT2 [63], which appear to precede demyelination, were also observed [134]. The pathological findings in patients with multiple sclerosis were in contrast to the findings in NMO patients; complement was deposited along myelin sheaths or within macrophages, and aquaporin-4 loss occurred only in end-stage lesions that had undergone widespread destruction [134].

Some aspects of NMO pathology have been recapitulated in animal models, but only where serum from NMO patients was injected intravenously or intraperitoneally into rats where blood–brain barrier was already compromised by the inflammatory sequelae of experimental autoimmune encephalomyelitis [15, 20, 78], or where patient NMO-IgG and human complement were co-injected directly into the cerebral hemispheres of mice [137].

Glycine receptor antibody

Antibody targeting the α1 subunit of the glycine receptor has been recently reported in a small number of GAD65 antibody-seronegative patients with disorders characterized by excessive startle, myoclonus, encephalopathy and

myelopathy. Associated neurological diagnoses have included progressive encephalomyelitis with rigidity and myoclonus (PERM, a rapidly progressive and usually fatal disorder) and atypical forms of stiff-man syndrome [69, 99, 122]. Glycine receptors are strychnine-sensitive chloride channels that mediate inhibitory synaptic transmission between interneurons and motor neurons in spinal cord reflex circuits. They are concentrated in olfactory bulb, retina, hippocampus, cerebellum, as well as in brainstem, and spinal cord [96]. There are 5 subunits (α1–4 and β) which have some homology with nicotinic AChRs. Heteromeric α1β GlyRs mediate most glycinergic neurotransmission in adults. Similar to the reported neurological phenotype associated with glycine receptor antibodies, mutations in the α1 subunit of the glycine receptor gene *GLRA1* have been identified in hereditary hyperekplexia, a disorder also characterized by exaggerated startle reflexes [145]. Irreversible binding of the rodenticide strychnine to glycine receptors results in severe muscle rigidity and spasms, seizures resulting in rhabdomyolysis followed rapidly by renal failure and death [117]. Cancer has been reported to date in just one patient (Table 2), and larger studies will need to be conducted to assess for potential oncological associations. Small-cell carcinoma cell lines are known to express the α1 subunit of glycine receptors [60].

One patient with SMS and an undifferentiated mediastinal carcinoma was reported to have antibodies targeting gephyrin, a cytosolic protein associated with $GABA_A$ and glycine receptors concentrated at the postsynaptic membrane of inhibitory synapses [25].

Conclusion

The rapidly evolving clinical and scientific field of paraneoplastic neurological disorders is yielding multiple autoantibody discoveries which enhance diagnostic patient evaluations. Identification of antigenic targets of those antibodies, correlated with neuropathological findings and experimental immunological studies facilitates a greater understanding of disease mechanisms. Improved understanding of disease mechanisms may permit development of novel immunotherapeutic strategies for paraneoplastic neurological disorders.

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