CLASSIC PARANEOPLASTIC NEUROLOGICAL DISORDERS

Andrew McKeon, MD
Mayo Clinic College of Medicine,
Rochester, MN

Neurological autoimmunity is increasingly recognized as a cause of subacute-onset neurological disorders.[1] Diagnosis of these disorders is frequently based on detection of one or more neural-antigen specific antibody markers in serum or CSF. Some autoimmune neurological disorders arise as an aberrant, autoimmune attack, in the context of an appropriate immune response to systemic cancer, and are known as paraneoplastic neurological disorders. Some have been long recognized and are considered classic (e.g. sensory neuronopathy arising in a patient, seropositive for Hu antibody [ANNA-1] with occult small cell lung carcinoma). Others have been more recently recognized (e.g. encephalitis in a woman, seropositive for NMDA receptor antibody, with occult ovarian teratoma).[2]

Pathophysiological mechanisms In broad terms, paraneoplastic neurological disorders arise as a peripheral immune response against one or more autoantigens in the nervous system that are also expressed in tumors. Tumor immune surveillance in affected patients usually results in neoplasia being confined to the primary organ and to regional lymph nodes. The neurological attack, in contrast, can be devastating and can affect the central, peripheral or autonomic nervous systems. Tumor-targeted immune responses are initiated by onconeural proteins expressed in the plasma membrane, nucleus, cytoplasm or nucleolus of certain cancers. These antigens are also expressed in neurons or glia and thus are coincidental targets.

Antibodies detected in moat classic paraneoplastic disorders recognize intracellular antigens which are not accessible to immune attack *in situ*, but peptides derived from intracellular proteins are displayed on upregulated MHC class-I molecules after breakdown in the proteasome and in turn are targeted by peptide-specific cytotoxic T cells. Thus, while these antibodies serve as very specific diagnostic biomarkers (e.g., Purkinje cell cytoplasmic antibody type 1 [PCA-1, aka anti-Yo]), they are unlikely to be pathogenic (**Table 1**).[3] These antibodies have positive predictive values for very specific cancer types greater than 70%.[4] Studies of autopsied tissues and experimental studies suggest that these types of paraneoplastic neurological disorders are caused by CD8+ cytotoxic T cells.[3] The neurological deficits usually do not improve with treatment, although sometimes the clinical picture stabilizes post-oncological therapy.[5] Deaths from the complications of neurological disease (rather than from metastatic cancer) are common.

In contrast, antibodies directed at neural cell plasma membrane antigens (**Table 2**; e.g., NMDA receptors) are effectors through multiple mechanisms.[6, 7] Consistent with these antibodies being pathogenic, in vitro experiments and autopsy studies have demonstrated plasmablast, antibody and complement deposition brain in perivascular and parenchymal distributions. These more recently described antibodies have varying positive predictive values for cancer (e.g. <10% for glycine receptor antibody versus 50% or greater for antibodies targeting NMDA, AMPA and $GABA_B$ receptors.[8-11] The response to one or more of steroids, IVIg and plasma exchange is often excellent, with full neurological remission possible.[12]

Clinical disorders: Patients usually present with subacute onset of neurological dysfunction, which may be classic syndromes or multifocal and atypical. Certain disorders have been syndromically associated with particular autoantibody markers (e.g., a stiff-man like disorder and amphiphysin autoantibody). Other classic antibody-neurological disorder associations reported include: PCA-1 (anti-Yo) and cerebellar degeneration, Ma2 and brainstem encephalitis, ANNA-2 (anti-Ri) and opsoclonus-myoclonus syndrome and CRMP-5 IgG (anti-CV2) and chorea. However, in clinical practice, some disorders encountered are multifocal, and atypical presentations which fall outside of the classic descriptions may occur (**Tables**). The neurological presentation is often the first clue to the existence, or limited recurrence, of a cancer. Risk factors for a paraneoplastic or other autoimmune

neurological disorder include a personal or family history of cancer or autoimmune disease, and a smoking history.

Table 1. Findings among patients with neuronal nuclear or cytoplasmic antibodies and (mostly classic) paraneoplastic disorders.

Antibody	Antigen	Oncological association	Neurological presentations
ANNA-1	ELAVL (Hu)	Small-cell carcinoma	Limbic encephalitis, brainstem encephalitis, sensory autonomic and other peripheral neuropathies
ANNA-2	NOVA 1, 2 (Ri)	Small-cell carcinoma, breast adenocarcinoma	Dementia, limbic encephalitis, brainstem encephalitis, myelopathy, opsoclonus-myoclonus syndrome, 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	Mullerian/breast adenocarcinoma	Cerebellar ataxia, brainstem encephalitis, myelopathy, neuropathies
PCA-2	Unknown	Small-cell carcinoma	Limbic encephalitis, ataxia, brainstem encephalitis, Lambert-Eaton syndrome, peripheral and autonomic neuropathies
CRMP-5 IgG	CRMP-5	Small-cell carcinoma, thymoma	Cognitive disorders, 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
Recoverin antibody	Recoverin	Small cell carcinoma, neuroendocrine carcinomas	Retinopathy
GAD65 antibody*	GAD65	Thymoma; renal cell, breast or colon	Stiff-man syndrome, stiff-man phenomena, ataxia, seizures, limbic encephalitis, brainstem encephalitis,
GFAP antibody	α/ε isoforms	adenocarcinoma Teratoma	ophthalmoplegia, parkinsonism, myelopathy Meningoencephalomyelitis

*Not considered a classic paraneoplastic antibody; occasional cancer accompaniments only.

Assesment: Clinical evaluation, MR imaging, electrophysiology testing, and neuropsychometric testing can help document objective abnormalities. Further clues to a paraneoplastic etiology may be found on CSF evaluation. Elevated protein concentration (> 100 mg/dL), increased white cell count, abnormal numbers of CSF-exclusive oligoclonal bands, and elevated IgG index and synthesis rate are all supportive.

Table 2. Findings among patients with plasma membrane protein antibodies and (mostly non-classic) paraneoplastic disorders.

Antibody	Antigen	Oncological association	Neurological presentation
*VGKC-complex	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	GluN1	Ovarian teratoma	Anxiety, psychosis, seizures, amnestic syndrome, dyskinesia, hypoventilation, coma.
AMPA receptor	GluR1,2	Thymic tumors, lung carcinomas, breast carcinoma	Limbic encephalitis, nystagmus, seizures

GABA-B receptor	GABA-B receptor	Small-cell lung carcinoma, other neuroendocrine neoplasia	Limbic encephalitis, intractable seizures, orolingual dyskinesias
PCA-Tr	DNER	Hodgkin lymphoma	Cerebellar ataxia
*P/Q and N type calcium channel	P/Q and N-type calcium channels	Small-cell carcinoma, breast or gynecological adenocarcinoma	Encephalopathies, myelopathies, neuropathies, Lambert-Eaton syndrome
Muscle AChR	Muscle AChR	Thymoma, thymic carcinoma, lung carcinoma	Myasthenia gravis. Also sometimes observed in paraneoplastic CNS contexts.
*Neuronal ganglionic AChR	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	α1 subunit GlyR	Thymoma, lymphoma	Stiff-man syndrome and variants
Metabotropic glutamate receptor 1	mGluR1	Hodgkin lymphoma, prostate adenocarcinoma	Ataxia, dysgeusia, vertigo, cognitive symptoms, seizures
Metabotropic glutamate receptor 5 antibody	mGluR5	2 patients with Hodgkin lymphoma	Limbic encephalitis

*Occasional cancer accompaniments only.

Autoantibody Testing:

The detection of a neural-specific antibody in serum or CSF aids the diagnostic process by increasing suspicion for a paraneoplastic cause. Antibody tests performed on serum alone are often sufficiently informative, but CSF testing sometimes increases the diagnostic yield (e.g. collapsin-response mediator protein 5 [CRMP5]-IgG).[13] However, in the case of NMDA-R and GFAP antibodies, CSF is more informative than serum.[14, 15]

Testing for Cancer: Certain antibodies with a particular cancer specificity (e.g. ANNA-1 and small cell carcinoma) may refine the oncological evaluation to one test in some patients. Testing may include one or more of CT of chest, abdomen, and pelvis, mammography in women, and testicular ultrasound and prostate-specific antigen (PSA) in men. Chest and abdominal CT or MRI, and urine testing for homovallinic acid metabolites should be undertaken in children where neuroblastoma is suspected. PET imaging alone, or in combination with anatomic data (PET-CT), increases the cancer diagnostic yield by 20% when all standard evaluations (e.g. whole-body CT scan) have been uninformative[16]. However, PET imaging is not helpful for detecting gonadal tumors (ovary or testis), neuroblastoma, or thymoma. MRI imaging has good sensitivity for both ovarian and thymic neoplasms.

Treatment: Randomized-controlled treatment trials for paraneoplastic neurological disorders are unavailable, and data pertaining to treatment is mostly derived from expert opinion, large case series and anecdotal reports.[17] The treatment of paraneoplastic neurological disorders consists of treating the underlying cancer which can result in stabilization of neurological decline or sometimes improvement. Some patients prove immunotherapy-responsive with steroids, IVIg or plasma exchange. Cyclophosphamide or rituximab may have a role in some patients in whom oncological therapy has been completed, yet progression of neurological symptoms continues.

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