AUTOIMMUNE BRAINSTEM DISORDERS, ATAXIAS AND MYELOPATHIES

Andrew McKeon
Mayo Clinic College of Medicine
Rochester, MN

Details regarding pathophysiology, evaluation and treatment of autoimmune neurological disorders in general can be found in the syllabus for Autoimmune Neurology I.

Neurological phenotypes

Brainstem encephalitis
The neurological manifestations of brainstem encephalitis are diverse, and may include one or more symptoms of subacute onset. Neuro-ophthalmologic symptoms may include eyelid ptosis, anisocoria, diplopia (due to skew deviation or ophthalmoparesis), oscillopsia (due to nystagmus or opsoclonus) and limited movement (due to supranuclear gaze palsies). A syndrome that is uniquely autoimmune is opsoclonus-myoclonus syndrome.[1] Vertigo, dysequilibrium and nausea may be early brainstem encephalitis symptoms. Nausea, hiccoughs and vomiting may also be indicative of medullary disease; those occurring in isolation over several weeks are the herald of neuromyelitis spectrum disorders in 12% of aquaporin-4 antibody positive cases.[2] Postural instability, parkinsonism and gait ataxia are common findings among patients with brainstem encephalitis. Disorders may mimic neurodegenerative conditions such as progressive supranuclear gaze palsy or multiple system atrophy.[3-5] If the pons is affected, appendicular cerebellar signs may be encountered also. The nuclei of one or more of cranial nerves III-XII may be potentially affected also. Sleep disorders (central sleep apnea, REM sleep behavior disorder, narcolepsy and cataplexy) may also occur.[5]

Cerebellar ataxias
These disorders often overlap with brainstem encephalitis, and frequently present with vertigo, nausea and vomiting before the emergence of more typical appendicular ataxic signs and a gait disorder. PCA-1 (anti-Yo) autoimmunity may present in this fashion. Unlike hereditary ataxias and most multiple system atrophy cases, autoimmune ataxias generally have subacute onset and rapid progression.[6]

CNS hyperexcitability
Autoimmune CNS hyperexcitability encapsulates a spectrum of disorders of the brainstem and spinal cord caused by dysfunction of GABAergic and glycinergic inhibitory interneurons. These disorders include classic stiff-person syndrome, limited forms of stiff-person (such as stiff-limb syndrome) and a more diffuse encephalomyelitis known as progressive encephalomyelitis with rigidity and myoclonus (PERM).[7]

Myelopathies
Patients with autoimmune myelopathy present with subacute onset and rapid progression of weakness and numbness, often ascending, and often accompanied by neuropathic pain in the extremities and trunk. Bowel and bladder dysfunction are common. Extremity and truncal wall spasms may be severe, and may be a clue to a diagnosis of CNS aquaporin-4 autoimmunity (neuromyelitis optic spectrum disorder).[2] Disability from spinal cord disease in the context of neuromyelitis optica is generally myelitis-attack related, thus stability is possible if attacks are prevented.[2] In contrast, paraneoplastic myelopathies tend to be progressive and have a poor prognosis.[8] The differential diagnosis for autoimmune myelopathy includes sarcoidosis of the CNS, degenerative disc disease causing cord compression with enhancement, multiple sclerosis, vitamin deficiency states (B12, folate, copper,

vitamin E, which may occur for a variety of reasons including untreated celiac disease), a dural arteriovenous fistula causing cord edema (which can mimic longitudinally-extensive transverse myelitis radiologically) and multiple sclerosis.

Examples of antibodies associated with brainstem disorders, ataxias or myelopathies.

The details of antibodies, neurological and cancer associations can be found in the **Table**.

Ma1and Ma2 antibodies
Ma1 and Ma2 have been described in association with encephalitis affecting primarily the mesial temporal lobes, diencephalon, brainstem and cerebellum.[9] Patients seropositive exclusively for Ma2 antibody are usually men, have germ cell tumors of testis, and can have improved neurological symptoms with cancer treatment. Patients seropositive for Ma1 and Ma2, are more often women, have cancer types other than germ cell testicular tumors (including adenocarcinomas of breast, colon, or ovary) and generally have a worse neurological outcome.

GAD65 neurological autoimmunity
GAD65 antibody is a sensitive and specific marker of type 1 diabetes. GAD65 antibody is also often detected in patients with autoimmune neurological disorders, but at antibody values much higher than in patients with type 1 diabetes alone (>20 nmol/L, versus usually <2.00 nmol/L). Neurological presentations include painful spasms and stiffness primarily affecting the lumbar spine and lower extremity musculature (stiff-person syndrome), brainstem disorders, extrapyramidal disorders including cerebellar ataxia, limbic encephalitis and epilepsy.[4, 7, 10] GAD65 antibody-associated neurological disorders occur more commonly in an idiopathic autoimmune context, but paraneoplastic cases have also been reported (including carcinomas of breast, thyroid, colon and kidney, and thymoma).[11]

Glycine receptor autoimmunity
Antibody targeting the α1 subunit of the glycine receptor was initially reported in a small-number of GAD65 antibody seronegative patients with PERM, which is rapidly progressive and usually fatal if not promptly treated.[12] Glycine receptor antibody is also detected in 12% of patients with stiff-person syndrome, including 25% of GAD65 antibody seronegative cases.[13] Glycine receptor antibody positivity may be predictive of immunotherapy responsiveness in stiff-person syndrome.[13]

Aquaporin-4 antibody and MOG antibody
Transverse myelitis is a syndrome common to autoimmunity targeting aquaporin-4 or MOG.[2, 14] In both, patients frequently present with severe myelitis, with longitudinally-extensive lesions on MRI imaging (3 or more vertebral segments of T2 signal abnormality). Both disorders are also associated with relapsing inflammatory CNS attacks, optic neuritis and sometimes encephalitis. MOG antibody has been detected in some patients with acute disseminated encephalomyelitis (ADEM), a monophasic severe diffuse inflammatory CNS disorder. Aquaporin-4 autoimmunity may also present in children with an ADEM-like illness, though those patients tend to have a relapsing course with more typical attacks (optic neuritis or transverse myelitis later on).[15] Sixteen percent of children with aquaporin-4 autoimmunity present with brain or brainstem symptomatology.

Table. Neurological and oncological findings among patients with autoimmune brainstem, ataxic or spinal cord 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, jaw dystonia, myelopathy, opsoclonus-myoclonus syndrome, peripheral neuropathy
ANNA-3	Unknown	Aerodigestive carcinomas	Brainstem encephalitis, limbic encephalitis, myelopathy, peripheral neuropathy
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, cranial neuropathies, 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-person syndrome, stiff-person phenomena, ataxia, seizures, limbic encephalitis, brainstem encephalitis, ophthalmoplegia, parkinsonism, myelopathy
VGKC- complex	CASPR2	Thymoma	Brainstem encephalitis, ataxia, extrapyramidal disorders, myoclonus, peripheral and autonomic neuropathy
DPPX	DPPX	B-CLL, lymphoma	Encephalopathy, tremor, myoclonus, gastrointestinal dysmotility
IgLON5	IgLON5	Unknown	Sleep disorders, respiratory failure, brainstem encephalitis, parkinsonism, ataxia
$GABA_B$-R	$GABA_B$-R	Small cell carcinoma	Limbic encephalitis, ataxia, myelopathy
Glycine receptor	α1 subunit GlyR	Thymoma, lymphoma	Stiff-man syndrome and variants
mGluR1	mGluR1	Hodgkin lymphoma, prostate adenocarcinoma	Ataxia, dysgeusia, vertigo, encephalopathy
Homer-3	Homer-3	None	Ataxia
ITPR1	ITPR1	Non-small cell carcinoma	Ataxia
CARP VIII	CARP VIII	Melanoma, ovarian adenocarcinoma	Ataxia
Anti-Ca/ARGHAP26	ARGHAP26	Ovarian adenocarcinoma	Ataxia, limbic encephalitis
PCA-Tr	DNER	Hodgkin lymphoma	Ataxia
MOG	MOG	None	Optic neuritis, myelitis, ADEM
NMO-IgG	Aquaporin-4	Some reports of thymoma and other solid tumors	Relapsing optic neuritis, transverse myelitis, encephalopathies

References

1. Klaas JP, Ahlskog JE, Pittock SJ, et al. Adult-Onset Opsoclonus-Myoclonus Syndrome. Arch Neurol 2012:1-10.
2. Wingerchuk DM, Lennon VA, Lucchinetti CF, Pittock SJ, Weinshenker BG. The spectrum of neuromyelitis optica. Lancet Neurol 2007;6:805-815.
3. Sabater L, Gaig C, Gelpi E, et al. A novel non-rapid-eye movement and rapid-eye-movement parasomnia with sleep breathing disorder associated with antibodies to IgLON5: a case series, characterisation of the antigen, and post-mortem study. The Lancet Neurology 2014;13:575-586.
4. Pittock SJ, Yoshikawa H, Ahlskog JE, et al. Glutamic acid decarboxylase autoimmunity with brainstem, extrapyramidal, and spinal cord dysfunction. Mayo Clin Proc 2006;81:1207-1214.
5. Adams C, McKeon A, Silber MH, Kumar R. Narcolepsy, REM sleep behavior disorder, and supranuclear gaze palsy associated with Ma1 and Ma2 antibodies and tonsillar carcinoma. Arch Neurol 2011;68:521-524.
6. Jones AL, Flanagan EP, Pittock SJ, et al. Responses to and Outcomes of Treatment of Autoimmune Cerebellar Ataxia in Adults. JAMA Neurol 2015;72:1304-1312.
7. McKeon A, Robinson MT, McEvoy KM, et al. Stiff-man syndrome and variants: clinical course, treatments, and outcomes. Arch Neurol 2012;69:230-238.
8. Flanagan EP, McKeon A, Lennon VA, et al. Paraneoplastic isolated myelopathy: clinical course and neuroimaging clues. Neurology 2011;76:2089-2095.
9. Dalmau J, Graus F, Villarejo A, et al. Clinical analysis of anti-Ma2-associated encephalitis. Brain 2004;127:1831-1844.
10. Quek AM, Britton JW, McKeon A, et al. Autoimmune epilepsy: clinical characteristics and response to immunotherapy. Arch Neurol 2012;69:582-593.
11. Arino H, Hoftberger R, Gresa-Arribas N, et al. Paraneoplastic Neurological Syndromes and Glutamic Acid Decarboxylase Antibodies. JAMA Neurol 2015;72:874-881.
12. Carvajal-Gonzalez A, Leite MI, Waters P, et al. Glycine receptor antibodies in PERM and related syndromes: characteristics, clinical features and outcomes. Brain 2014;137:2178-2192.
13. McKeon A, Martinez-Hernandez E, Lancaster E, et al. Glycine receptor autoimmune spectrum with stiff-man syndrome phenotype. JAMA Neurol 2013;70:44-50.
14. Reindl M, Di Pauli F, Rostasy K, Berger T. The spectrum of MOG autoantibody-associated demyelinating diseases. Nat Rev Neurol 2013;9:455-461.
15. McKeon A, Lennon VA, Lotze T, et al. CNS aquaporin-4 autoimmunity in children. Neurology 2008;71:93-100.