Newer Investigations in Autoimmune Neurological Conditions

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Introduction

O

n the last two decades, the role of auto-immunity in the etiopathogenesis of various neurological disorders has been increasingly recognised. In fact, this area of neurology is one of the fastest evolving, in terms of discovery of new antibodies and their association with hitherto ‘idiopathic’ clinical syndromes, and the application of immunomodulatory treatments.

In this article, we discuss a syndromic approach to clinical recognition of a possible autoimmune/paraneoplastic involvement of specific areas of the CNS/PNS (with the omission of muscle disorders), along with relevant laboratory investigations, the association of underlying neoplasia or a systemic autoimmune disease with these syndromes, and the investigation pathway thereof.

Autoimmune and paraneoplastic encephalitis

Encephalitis implies fever with acute or subacute confusion and cognitive dysfunction, with or without seizures and focal deficits. Encephalopathy (without fever) could result from metabolic disorders, vascular causes, toxins, neoplasia, and nutritional imbalances. In the search for an etiological cause in Encephalopathy/Encephalitis, Autoimmune encephalitis is being increasingly recognised as a putative etiology. Recently proposed criteria use clinical and serological testing for diagnosis of autoimmune encephalitis in the correct setting.

Limbic Encephalitis

The limbic system comprises the Cingulate gyrus, Para hippocampal gyrus, dentate gyrus, Hippocampus, Subicular Complex, Amygdala, septal area and hypothalamus. Limbic encephalitis (LE) is characterised by rapidly progressive personality and behaviour changes, seizures, memory loss, depression, irritability and occasionally, dementia. The classical prototype of Limbic encephalitis is HSV-1 infection.

When these symptoms are seen in young women along with unilateral focal movements, psychosis, catatonia, seizures, myoclonus, behaviour disturbances and dysautonomia, then one should suspect anti-NMDA-R antibody related encephalitis. Focal movements are unilateral and predominantly involve the upper limb, resembling epilepsy partialis continua (EPC) (other presentations are dystonia, choreoathetosis and myorhythmia). NMDAR has a female preponderance. Clinical criteria for NMDA-R antibody related encephalitis diagnosis include:

1. Rapid onset (under 3 months) of at least four of the six following major groups of symptoms:
   - Abnormal behaviour or cognitive dysfunction
   - Speech dysfunction (pressured speech, verbal reduction, mutism)
   - Seizures
   - Dyskinesias, or rigidity/abnormal postures
   - Decreased level of consciousness
   - Autonomic dysfunction or central hypoventilation

2. At least one of the following laboratory study results:
   - Abnormal EEG (focal or diffuse slowing or disorganised activity, epileptic activity, or extreme delta brush)
   - CSF with pleocytosis or oligoclonal bands

3. Reasonable exclusion of other disorders (Infectious encephalitis, cerebral vasculitis, Wernicke’s encephalitis, Hashimoto’s encephalitis)

Diagnosis can be made when i) All three criteria have been fulfilled or ii) presence of one or more of the six major clinical symptoms with positive CSF NMDA-R antibody.

In upto 50% of patients, MRI brain may show T2 or FLAIR signal hyperintensity in the hippocampi, cerebellar or cerebral cortex, frontobasal and insular regions, basal ganglia, brainstem and infrequently, the spinal cord.

Around 20-40% patients have a neoplasm at diagnosis, ovarian teratomas being the commonest. Teratomas are present in 15% of female patients under 14 years, in 30% of those under 18 years and in 60% of those over 18 years of age. Frequency of underlying tumour is less after 45 yrs of age. It is recommended to screen for a pelvic tumour by MRI every 6 months for 4 yrs, if initial tests are negative.

Anti-NMDA-R antibody is detected by cell-based assay (CBA) or tissue-based assay (Immunohistochemistry-IHC). Both IHC and CBA assays are 100% specific in the serum and CSF. The CSF is more sensitive than serum by both IHC (100% vs 92% respectively) and CBA (100% vs 87% respectively). High CSF titre is associated with poor prognosis and relapse.

Limbic encephalitis presenting in an older age group, should make one consider anti-AMPA-R (α-amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid receptor) antibody-related encephalitis. It has female preponderance, with average age of presentation being 62 yrs. Association with lung and breast carcinoma is seen in 60-70% of patients. CSF may show lymphocytic pleocytosis. MRI brain may show unilateral or bilateral mesiotemporal (FLAIR)/T2 hyperintense signal abnormalities. EEG features may include diffuse slowing or focal/generalised epileptiform activity. CSF testing for anti-AMPAR-ab, by IHC or CBA, is more sensitive as compared to serum.

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Limbic encephalitis in an elderly male with typical dystonic seizures, hyponatremia (in 60%) and insomnia may be due to anti-LGI1 (anti-leucine-rich glioma-inactivated 1)-antibody subtype of anti-VGKC-(voltage-gated potassium channels) antibody.\textsuperscript{16,17} There are no specific diagnostic criteria. Upto 23% patients with encephalitis may show CSF pleocytosis and raised proteins.\textsuperscript{18} T2W hyperintensities in medial temporal region on MRI brain are seen in 84% patients.\textsuperscript{19} EEG may be normal or show mild diffuse slowing.\textsuperscript{19} Most studies have concluded that testing anti-LGI1 antibodies in serum is more sensitive than in CSF.\textsuperscript{20,21} Antibodies can be detected by RIA, IHC or CBA, the last being most sensitive.\textsuperscript{13}

The entity previously known as Hashimoto’s encephalitis and now termed as steroid-responsive encephalopathy associated with autoimmune thyroiditis (SREAT) is characterised by acute to subacute onset repeated focal neurological deficits with cognitive dysfunction and altered mental status.\textsuperscript{22} It has a female preponderance. Seizures, myoclonus, psychosis and bipyramidal signs have been described in SREAT.\textsuperscript{23,24} The relation to anti-TPO (Thyroid peroxidase) is debatable, other biomarkers mentioned being anti-enolase and anti-thyroglobulin.\textsuperscript{22} Anti-TPO testing has higher sensitivity in serum as compared to CSF, and does not predict severity or treatment response.\textsuperscript{24}

Autoimmune psychosis

Diagnostic difficulties arise when a psychiatric manifestation is the presenting complaint in an autoimmune condition. Clinical spectrum of such psychiatric manifestations includes autism spectrum disorder, schizophrenia, bipolar disorders and obsessive-compulsive disorders.\textsuperscript{25} One should suspect psychiatric manifestations are of autoimmune origin when there is drug resistance, atypical age of onset, multimodal hallucinations, confusion, language disintegration, antecedent or concurrent medical illness and lack of predisposing risk factors for psychiatric illness.\textsuperscript{26} Antibodies targeting NMDA-R, LGI1, CASPR2, AMPA-R, GABA\textsubscript{A}-R, and dopamine-2-receptor are commonly associated with psychiatric manifestations.\textsuperscript{27}

**Brainstem syndromes**

An autoimmune encephalitis which specifically targets the brainstem is Bickerstaff encephalitis (BE)\textsuperscript{28} which is due to anti-GQ1b related antibody and is characterised by subacute onset altered consciousness, ophthalmoplegia and ataxia.\textsuperscript{27} It has an overlap with Miller-Fischer syndrome.\textsuperscript{29} Proposed diagnostic criteria for Bickerstaff encephalitis include\textsuperscript{8}

A. Probable diagnosis, when both of the following criteria have been met:

1. Subacute onset (rapid progression under 4 weeks) of all of the following:
   - Decreased level of consciousness
   - Bilateral external ophthalmoplegia
   - Ataxia

2. Reasonable exclusion of alternative causes (Listeria monocytogenes, Enterovirus 71 encephalitis in children, paraneoplastic and post infectious brainstem encephalitis, chronic lymphocytic encephalitis with pontine perivascular enhancement responsive to steroids (CLIPPERS), neurosarcoidosis, Wernicke’s encephalopathy and primary CNS lymphoma).\textsuperscript{6}

B. Definite Bickerstaff’s brainstem encephalitis:

A definite diagnosis can be made if clinical criteria are met, and positive IgG anti-GQ1b antibodies are detected. The utility of anti-GQ1b-\textsubscript{ab} detection is 92% and specificity is 97% in serum, while in CSF, sensitivity is 20% and specificity 100%. Other less commonly used methods of antibody detection include immunodot-assay, flowcytometry and cell surface binding, and glyco-array.\textsuperscript{30} MRI may show T2 hyperintense lesion in brainstem, thalamus, cerebellum or white matter of the cerebrum.\textsuperscript{29,32} EEG may demonstrate \(\theta\) or \(\delta\) activity at rest.\textsuperscript{28}

In the presence of brainstem syndrome characterised by sleep disorders (sleep apnoea, parasomnia, insomnia, daytime sleepiness), bulbar symptoms (dysphagia, bulbar dystonia, sialorrhea, respiratory dysfunction, vocal cord palsy), gait imbalance/ initiation difficulties and various supranuclear gaze palsy resembling PSP, chorea and cognitive dysfunction, one should suspect anti-IgLON5\textsuperscript{33,34} related disease. Incidence is almost same in males and females.\textsuperscript{20,21} CSF examination and MRI are largely normal.\textsuperscript{32,31} In a study of 20 patients, serum was available for testing in 19 and CSF in 8; all specimens were positive for IgLON5-IgG by both IFA and CBA.\textsuperscript{32}

Paraneoplastic cerebellar degeneration

The clinical presentation of these disorders includes acute to subacute onset nausea, vomiting, dizziness, limb and truncal ataxia, dysarthria and diplopia, seen predominantly in an older age group.\textsuperscript{33,34} Table 1 enumerates the associated neurological features which may offer a clue to the possible tumour biomarkers.

Autoimmune Epilepsy

Although seizures may be a part of the spectrum of autoimmune encephalitis, at times they may be the single presenting feature of an autoimmune disease.\textsuperscript{29} Clues to diagnose autoimmune epilepsy include acute or subacute onset (<3 months), multiple seizure types, high frequency of seizures, resistance to anti-epileptics, history of or features suggesting underlying autoimmune condition, presence of underlying neoplasia, family history of any autoimmune conditions and a viral prodrome.\textsuperscript{39} A good response to steroid therapy also supports the diagnosis.\textsuperscript{38} Table 2 details the clinical and investigative characteristics of these Seizures.

Autoimmune movement disorders

An autoimmune etiology may be considered if the movement disorder is acute or subacute in onset with rapid progression, with associated neurological features like encephalitis, brainstem syndrome, dysautonomia, psychosis, sleep disorders, seizures and ataxia.\textsuperscript{40} Autoimmune movement disorders may be classified into akinesthesias and dyskinesias.

A. Akinetid rigid syndrome: The prototype of this is stiff person syndrome. Clinical features of this disease include progressive muscular stiffness, episodic
painful muscle spasms and startle reflex.5,75 Characteristic syndromes with the above features are included in stiff person syndrome spectrum disorder (SPSSD). SPSSD includes classic stiff person syndrome (SPS) and stiff limb syndrome (SLS), progressive encephalomyelitis with rigidity and myoclonus (PERM) and stiff person plus syndromes (SPPS).46,45 Table 3 enumerates the clinical syndromes and their associations.

B. Autoimmune dyskinetic movement disorders: Dyskinesiasare involuntary, abnormal movementsspanning a wide range of clinical subtypes. Table 4 enumerates the movement disorders associated with certain autoimmune antibody types.47,45,48,44

Autoimmune myelopathy In the setting of an acute or subacute onset para/quadriparesis which involves a large transverse extent of the cord and where infective, vascular, toxic and structural causes have been ruled out, an antibody related demyelinating disorder can be considered.49

MRI of the cord/brain serves to rule out vascular, infective and structural causes of these syndrome and confirms the presence of long segment signal abnormality on T2W (≥3 segments), with or without spinal cord swelling. It is important to take history of recent vaccination in previous three weeks and look for evidence of infective myelitis, before concluding that it is an antibody associated myelopathy.50,49 In this context it is important to mention that spinal cord involvement in multiple sclerosis is characterised by short segment (2 or less) involvement, transversely affecting eccentric/lateral parts of cord only, with no spinal cord swelling.51

Table 5 shows the difference between aquaporin 4 and MOG antibody related myelopathy. Additionally, the pattern of associated brain and optic nerve involvement gives the clue to etiology in NMO (Neuromyelitis Optica spectrum disorder)- viz. the aquaporin 4 antibody associated NMO or MOG (Myelin Oligodendrocyte glycoprotein) antibody associated NMO.32

The extended spectrum of NMO which is now defined by criteria includes involvement of the area postrema (persistent hic cus and vomiting), hypothalamus (narcolepsy, dyshermia, dystautonomia), and a brainstem syndrome.52 By and large, physicians would see patients presenting with a spinal cord syndrome and identify the associated cerebral involvement only on pointed questioning and brain imaging. The aquaporin antibody specifically targets antigens around CSF channels in the brain and hence results in the typical presentation.53 On the other hand, MOG-Ab related NMO has a very varied presentation in the brain which can be Encephalopathic / brainstem syndromes or seizures.54

For detecting AQP4-antibody, cell-based assay has 100% specificity and 68% sensitivity while ELISA has specificity of 100% and sensitivity of 60%; sensitivity is 72% when used in combination.61 Antibody testing in serum is more sensitive than CSF.53,61 Detection of Anti-MOG antibody is done by CBA in serum which is highly specific and sensitive; previously used ELISA method is not recommended due to high false positive results.52,65

The clinical spectrum of Acute Demyelinating Encephalomyelitis (ADEM) includes encephalopathy with or without seizures following vaccination or infection in young children.49 MRI shows widespread involvement of brainstem, thalamus, cortex with uniform enhancement on contrast with or without spinal cord demyelination.64 Up to half of ADEM presentation in children has now been shown to have a serum positivity for MOG antibody.55,66

Autoimmune neuropathy Disorders related to autoimmune neuropathy include those affecting Neuronal cell body i.e. neuronopathy and those affecting peripheral nerves, i.e. peripheral neuropathy. Clinical approach depends on types of fibres involved, pattern of fibres involved (mononeuropathy, polyneuropathy, mononeuritis multiplex); temporal evolution- acute, subacute and chronic; course of disease- monophasic or relapsing remitting, and family history suggestive of neuropathy. Nerve conduction and electromyography findings confirm the pattern and nerve fibre type, besides delineating the pathology as axonal or demyelinating. Presence of additional systemic disorders like paraproteinemia, neoplasia, vasculitis, nutritional deficiencies, drug and toxin exposure, and personal history suggestive of autoimmune etiology will help to narrow down the differential diagnoses.

In the presence of acute onset symmetrical (usually ascending) areflexic flaccid paraparesis/quadriaparesis with or without cranial nerve involvement (occasionally a pure cranial nerve involvement) with preceding history of fever, upper respiratory tract/ gastrointestinal infection or recent vaccination, one should suspect Guillian–Barré syndrome (GBS). Differentiation between different subtype of GBS depends on clinical presentation and electrophysiological findings.67 Albumino-cytological dissociation in CSF is present later in the course, usually after two weeks of illness (in 80% patients).68 Table 6 enumerates the different subtypes of GBS.

There has been no study to demonstrate any difference in response to immunomodulatory treatments, based on specific antibody subtype of GBS.71

In the presence of a clinical syndrome with slowly progressive or relapsing remitting weakness (more than 8 weeks), causing both proximal and distal motor involvement, rarely involving bulbar, autonomic and respiratory systems, one should suspect chronic inflammatory demyelinating polyneuropathy (CIDP).69,67 NCS findings include a) prolonged distal motor latency and slow conduction velocity, b) Prolonged F wave latency, c) Conduction blocks, and d) Temporal dispersion. CSF shows albumino-cytological dissociation.57,66 Nerve biopsy may show myelin lamellar collagen thickenings (onion Bulb appearance) with mononuclear infiltrates in both endoneurium and epineurium.69 Auto antibodies associated with CIDP are anti-contactin (aggressive course, initial axonal loss), anti-NF155 (Tremors, ataxia and distal motor involvement), anti-NF186 and anti-NF140 (Subacute onset, sensory axonopathy). Clinical pattern of CIDP with a pattern of distal upper limb and lower limb symmetrical sensory motor polyneuropathy with prominent sensory symptoms, with evidence of demyelination in motor and sensory nerves on NCS is the distal acquired demyelinating sensory (DADS) neuropathy.72,67 IgM gammopathy and anti-MAG antibody
are associated, in approximately two-thirds of patients with DADS. Other variants of CIDP such as Multifocal Acquired Demyelinating Sensory and Motor Neuropathy (MADSAM) and Chronic immune sensorypolyradiculopathy (CISP), are rarely associated with anti-GM1 antibody.75

In the presence of clinical features of subacute onset asymmetrical lower motor neuron weakness in a nerve distribution, involving distal arm(61%) or distal leg(34%) with sparing of sensory, bulbar, autonomic and respiratory systems and NCS finding of conduction blocks, one should suspect Multifocal Motor Neuropathy (MMN). 74

Table 1: Paraneoplastic cerebellar syndromes

<table>
<thead>
<tr>
<th>Associated neurological features besides cerebellar signs</th>
<th>Antibody</th>
<th>Associated Tumour</th>
</tr>
</thead>
<tbody>
<tr>
<td>Peripheral neuropathy 33,34</td>
<td>Anti-Yo (PCA1) (in 100% patients)</td>
<td>90% - Breast, Ovarian or Lung neoplasm</td>
</tr>
<tr>
<td>Sensory neuronopathy, cranial neuropathy, encephalomyelitis, seizures, opsoclonus-myoclonus34,35</td>
<td>Anti-Hu (Anti-ANNA1) (in 18% patients)</td>
<td>80% - Lung Cancer, Neuroblastoma</td>
</tr>
<tr>
<td>Opsoclonus-myoclonus, brainstem encephalitis37,38</td>
<td>Anti-Ri* (Anti-ANNA2) (in 86% patients)</td>
<td>60%-Breast, ovary, Lung Ca</td>
</tr>
<tr>
<td>*</td>
<td>Anti-Tr (in 100%)</td>
<td>85%</td>
</tr>
<tr>
<td></td>
<td>Anti-mGluR1</td>
<td>Hodgkin’s lymphoma</td>
</tr>
</tbody>
</table>

*Anti-Ri antibody associated cerebellar ataxia has less prominent nystagmus and dysarthria; Note: Cerebellar ataxia may be a feature of anti-GAD65 associated disorders.

Table 2: Autoimmune Epilepsies

<table>
<thead>
<tr>
<th>Seizure semiology</th>
<th>Associated features</th>
<th>MRI</th>
<th>EEG</th>
<th>CSF</th>
<th>Possible antibody</th>
</tr>
</thead>
<tbody>
<tr>
<td>Intractable focal seizures, Epilepsia partialis continua</td>
<td>Seen in Children, Progressive hemiparesis followed by encephalitis (Rasmussen encephalitis)</td>
<td>Unilateral hemispheric atrophy with T2 hyperintensity</td>
<td>Interictal epileptiform abnormalities and intermittent or continuous focal seizure activity over the affected hemisphere</td>
<td>Normal in more than 50%</td>
<td>Unknown</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>excess delta brush pattern</td>
<td>Pleocytosis in 80% patients</td>
<td>Anti-NMDAR</td>
</tr>
<tr>
<td>Complex partial, secondary generalised tonic clonic seizures</td>
<td>Young female, Psychosis, Catatonia, Dysautonomia, Dyskinesia, ± Ovarian teratoma</td>
<td>Usually normal. May have neocortical, medial temporal, basal ganglia hyperintensity</td>
<td>Interictal abnormalities localized to the temporal regions</td>
<td>Usually normal, moderate pleocytosis may be present</td>
<td>Anti-LGI</td>
</tr>
<tr>
<td>Facio-brachial dystonic seizures</td>
<td>Elderly male, Rapid cognitive decline, sleep behavioural disorders, hyponatremia</td>
<td>T2 hyperintensity and swelling in hippocampi (84%)</td>
<td>Generalised slowing with ictal activity in temporal or frontal region</td>
<td>Lymphocytic pleocytosis</td>
<td>Anti-GABA</td>
</tr>
<tr>
<td>Refractory seizures, status epilepticus</td>
<td>Children, Rapidly progressive encephalitis Thymoma (40%)</td>
<td>Multifocal cortical/subcortical T2/FLAIR abnormalities in temporal and frontal lobes</td>
<td>Generalised slowing with ictal activity in temporal or frontal region</td>
<td>Lymphocytic pleocytosis</td>
<td>Anti-GABA</td>
</tr>
<tr>
<td>Generalised tonic clonic seizures, status epilepticus</td>
<td>Median age 66yrs, Limbic encephalitis, ataxia, brainstem encephalitis, and opsoclonus-myoclonus syndrome Small cell lung carcinoma</td>
<td>Normal (50%)</td>
<td>Epileptiform abnormality. Or diffuse slowing</td>
<td>Mild lymphocytic pleocytosis</td>
<td>Anti-GABA</td>
</tr>
<tr>
<td>Generalised tonic clonic seizures</td>
<td>Elderly age, Cerebellar ataxia, Lung, Breast, gynaecological tumour</td>
<td>Cerebellar atrophy may be seen</td>
<td>Lymphocytic pleocytosis</td>
<td>Anti-Hu, Anti-mGluR1, Anti-GAD65</td>
<td></td>
</tr>
<tr>
<td>Generalised tonic clonic, complex partial seizures</td>
<td>Young age F&gt;M. Depression, Psychosis, Stroke, meningitis Systemic autoimmune manifestations-Discoid lupus rash, hair loss, recurrent skin or oral ulcers, Raynaud’ phenomenon</td>
<td>Focal T2 hyperintensity in affected part</td>
<td>Diffuse slowing</td>
<td>Lymphocytic pleocytosis</td>
<td>ANA, DS-DNA, (SLE)</td>
</tr>
</tbody>
</table>

The differential diagnosis of monomelic amyotrophy which can be seen in both Hirayama disease (a focal, largely benign amyotrophy of the upper limb, usually seen in young men), and amyotrophic lateral sclerosis (ALS) when it presents with a focal amyotrophic onset. MMN is a treatable condition with good response to IVIG whereas both Hirayama and ALS have no specific therapy. CIDP, DADS and axonal sensory motor neuropathy, especially in the elderly, should prompt a search for underlying paraproteinaemia, as treatment response of the neuropathy depends on treatment of the paraproteinaemia. Paraproteineinemic neuropathy can be seen in haematological diseases like multiple myeloma, Waldenstrom macroglobulinemia, cryoglobulinemia, amyloidosis and POEMS (Polyneuropathy, organomegaly, endocrinopathy, monoclonal gammopathy and skin changes). Paraproteineinemic neuropathy is most commonly seen with IgM gammopathy followed by IgG and...
The presence of acute or subacute onset painful, asymmetrical or multifocal weakness, in a predominant pattern of mononeuritis multiplex, most commonly involving distal leg, one should suspect vasculitis associated neuropathy. The pattern may also be of a sensory motor axonal neuropathy or sensory neuropathy. It may be associated with systemic or non-systemic vasculitis. NCS may show polyradiculoneuropathy. Nerve biopsy classically shows vasculitis with axonal degeneration and CSF examination is usually normal in these patients. Laboratory investigations to determine cause of vasculitis should be performed.

Paraneoplastic Neuropathy

Paraneoplastic neuropathy may present in a pattern of sensory or motor neuropathy, or sensory motor polyneuropathy with autonomic involvement. Early involvement of upper limbs has been described in motor forms. Constitutional symptoms and co morbidity of associated neoplasms with antibody markers confirms the diagnosis. Paraneoplastic neuropathy can be seen in association with Lung carcinoma (most common), thymoma, lymphoma and breast carcinoma. If a primary tumour is undetected, yearly screening is recommended. Anti-Hu (ANNA1) is the most common antibody associated with paraneoplastic neuropathy. Peripheral neuropathy can be seen in around 74% of patients with anti-Hu antibody, 67% having purely sensory neuropathy, 27% having sensory motor neuropathy and 7% having purely motor neuropathy. Other antibodies which can cause paraneoplastic neuropathy are anti-CRMP5, anti-ANNA2, anti-Aphiphysin, anti-Yo, anti-PAC1 and anti-VGKC.

<table>
<thead>
<tr>
<th>Antibody</th>
<th>Neurological features</th>
<th>Non-neurological features</th>
</tr>
</thead>
<tbody>
<tr>
<td>Anti-GAD65</td>
<td>SP5, ataxia, limbic encephalitis, epilepsy, ocularmotor disturbances, dysautonomia</td>
<td>Diabetes mellitus, vitiligo, thyroiditis, pernicious anaemia</td>
</tr>
<tr>
<td>Anti-Aphiphysin</td>
<td>SP5, Sensorly ganglioneopathy, myelopathy</td>
<td>Breast, small cell lung carcinoma</td>
</tr>
<tr>
<td>Anti-Glycine-R</td>
<td>PERM, SP5, Encephatia, dystonia, hyperkplexia, ophthalmotonus, opsoclonus-myoclonus, parkinsonism, tremor</td>
<td>Thymomas, lymphomas, small cell lung cancer and breast cancer</td>
</tr>
<tr>
<td>Anti-Glycine-R</td>
<td>SP5, Brainstem encephalitis, myelopathy</td>
<td>-</td>
</tr>
<tr>
<td>Anti-Dipeptidyl-peptidase-like protein-6 (DPPX)</td>
<td>Prolonged diarrhoea preceding SP5, encephalitis, ataxia, dysautonomia, cognitive decline,</td>
<td>B-cell tumour (in 7%)</td>
</tr>
<tr>
<td>Anti-GABA</td>
<td>Very few cases reported, SP5 with epilepsy, SLS</td>
<td>-</td>
</tr>
<tr>
<td>Anti-Ri</td>
<td>-</td>
<td>Breast, ovary, lung carcinoma</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Antibody/Syndrome</th>
<th>Neurological features</th>
<th>Non-neurological features</th>
</tr>
</thead>
<tbody>
<tr>
<td>Anti-NMDA</td>
<td>Choreaform movements, orofacial dyskinesia, ataxia, dysautonomia, stereotype, myoclonus</td>
<td>-</td>
</tr>
<tr>
<td>Anti-LGI-1</td>
<td>Faciobrachial dystonia, chorea, Parkinson’s</td>
<td>-</td>
</tr>
<tr>
<td>Anti-CASPR2</td>
<td>Morvan’s Neuromyositis, cramps, Fasciculation.</td>
<td>-</td>
</tr>
<tr>
<td>Sydenham’s chorea</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>Anti-Lysoglucoside, Anti-Tubulin, Anti-Dopamine-R1 and 2</td>
<td>Chorea, tics, hypotonia</td>
<td>-</td>
</tr>
<tr>
<td>Basal ganglia Encephalitis</td>
<td>Dystonia, Parkinson’s, chorea</td>
<td>-</td>
</tr>
<tr>
<td>Anti-Dopamine-R2</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>PANS (Paediatric Acute onset Neuropsychiatric syndrome)</td>
<td>Prepubertal onset of Tics, Choreaform movements with obsessive-compulsive disorder (OCD) and a relapsing and remitting course</td>
<td>-</td>
</tr>
<tr>
<td>Anti-Lysoglucoside, Anti-Tubulin, Anti-Dopamine-R1 and 2</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>Tourette Syndrome</td>
<td>Multiple motor and one or more vocal tics for over one year (DSM 5 criteria)</td>
<td>-</td>
</tr>
<tr>
<td>Anti-Dopamine-R2</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>Anti-IgLON-5</td>
<td>Severe gait instability, rapid periodic leg movements, chorea, mandibular spasms</td>
<td>-</td>
</tr>
<tr>
<td>Anti-AMPAR</td>
<td>Athetosis, chorea, dystonia, myoclonus, tremors</td>
<td>-</td>
</tr>
<tr>
<td>Anti-CRMP5/CV2</td>
<td>Ballism, Chorea, dystonia, tremors, opsoclonus-myoclonus</td>
<td>-</td>
</tr>
<tr>
<td>Anti-Ma2</td>
<td>Subacute Parkinson’s/Progressive supranuclear palsy, dystonia, Opsoclonus-myoclonus</td>
<td>-</td>
</tr>
<tr>
<td>Anti-GABA</td>
<td>Dystonia, Opsoclonus-myoclonus</td>
<td>-</td>
</tr>
<tr>
<td>Anti-GABA</td>
<td>Chorea, Opsoclonus-myoclonus</td>
<td>-</td>
</tr>
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Note: The syndromes have a broad spectrum of neurological manifestations, enumerated elsewhere in the article. Only the associated movement disorders are highlighted here.
In the presence of progressive proximal weakness and fatiguability generally sparing cranial musculature, associated with dysautonomia and uniformly depressed deep tendon reflexes (which may emerge after muscle exercise), one should suspect Lambert-Eaton Myasthenic Syndrome (LEMS), a presynaptic defect. It is more common in males. Sixty percent of LEMS cases are associated with small cell lung carcinoma and 50% may be associated with some underlying autoimmune etiology. On high frequency RNS, incremental response in CMAP is seen, corroborated by post exercise facilitation (Figure 1). Antibodies to P/Q type of VGCC are detected in 85-90% of LEMS patients, with a diagnostic sensitivity of 89% and specificity of 36% by RIA. The recently described SOX1 antibody has a sensitivity of 67% and a specificity of 95% to discriminate between LEMS associated with small cell lung carcinoma and non-tumour associated LEMS, by ELISA method.

Autoimmune channelopathies affecting the neuromuscular system may present to physicians with neuromyotonia (NMT) and the cramp fasciculation syndrome (CFS). NMT is a diverse disorder. As a result of muscular hyperactivity, patients may present with muscle cramps, stiffness, associated walking difficulties, hyperhidrosis, myokymia, fasciculations, fatigue, exercise intolerance and myoclonic jerks. Clinical examination may reveal continuous rippling of muscles at rest (myokymia). EMG reveals peripheral nerve hyperexcitability, and is not associated with abnormality of thymus. Anti-LRP4 is positive in 1-5% MG patients who are negative for ACRAB and MuSK antibodies. LRP4 associated MG commonly involves and remains restricted to Ocular muscles. CBA is a more sensitive method as compared to RIA and ELISA for NMJ related antibodies. Additionally, striational antibodies reacting with the epitope of muscle protein Titin and Ryanodine receptor (RyR) have been described in thymoma associated MG, and may correlate with higher severity of MG.

Table 5: The Spectrum of NMOSD-Differentiating anti-AQP4 and anti-MOG disorders

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Anti-AQP4</th>
<th>Anti-MOG</th>
</tr>
</thead>
<tbody>
<tr>
<td>Spinal cord involvement</td>
<td>Longitudinally extensive transverse myelitis, Central/Gray matter lesions, Hyperintense lesions on T2 and Hypointense on T1</td>
<td>Longitudinally extensive transverse myelitis (70%). Cervical(20%), thoracic(40%), cervicothoracic (40%) and conus involvement (40%).</td>
</tr>
<tr>
<td>Brain involvement</td>
<td>T2 hyperintensity in dorsal medulla especially area postrema, periependymal surface of brainstem, hypothalamus, thalamus, subcortical or deep white matter, corpus callosum, cerebral peduncle</td>
<td>Fluffy, poorly demarcated T2W hyperintense lesions, majority are bilateral and one third in subcortical region- more commonly in brainstem. Thalamic and pontine lesions more common in ADEM related to MOG-Ab. Cerebellar peduncle lesions are present only in MOG-Ab positive children when compared to NMOSD</td>
</tr>
<tr>
<td>Optic nerve</td>
<td>Predominantly Involves posterior segments, including the optic chiasm and prechiasmatic segment more frequently. Typically characterized as bilateral and longitudinally extensive optic nerve involvement more than half the length of the optic nerve is usually involved</td>
<td>A. Predominantly involves the anterior segments of the optic nerve and most commonly involves orbital segment. B. Inflammation and enhancement of the peri-optic nerve sheath, partly extending into the surrounding orbital fat, is often demonstrated (1/3 of cases)</td>
</tr>
<tr>
<td>CSF</td>
<td>Pleocytosis</td>
<td>Pleocytosis</td>
</tr>
<tr>
<td>Serum</td>
<td>Anti-AQP4 antibody+</td>
<td>Anti-MOG antibody+</td>
</tr>
<tr>
<td>Associated autoimmune condition</td>
<td>-Sjogren’s, -Systemic Lupus Erythematosus (SLE) -Myasthenia gravis</td>
<td>ADEM (acute demyelinating encephalomyelitis)</td>
</tr>
<tr>
<td>Age</td>
<td>Adult</td>
<td>Younger age</td>
</tr>
<tr>
<td>Prognosis</td>
<td>Relapsing course</td>
<td>Monophasic or relapsing course</td>
</tr>
</tbody>
</table>

Table 6: GBS- Correlation of clinical and electrophysiological subtypes with associated antibodies

<table>
<thead>
<tr>
<th>Characteristic Clinical and NCS findings</th>
<th>Syndrome</th>
<th>Possible antibody</th>
</tr>
</thead>
<tbody>
<tr>
<td>NCS- Delayed or absent H and F reflex are earliest findings. Slow conduction velocity in motor and sensory nerve conduction are seen in later course.</td>
<td>Acute inflammatory demyelinating radiculoneuropathy (AIDP)</td>
<td>Unclear</td>
</tr>
<tr>
<td>Only motor nerve involvement. Reduced compound muscle action potential on NCS</td>
<td>Acute motor axonal neuropathy (AMAN)</td>
<td>GM1, GM1b, GD1a and GalNAc-GD1a</td>
</tr>
<tr>
<td>Both sensory and motor nerves are affected, with severely reduced or absent motor and sensory potentials</td>
<td>Acute motor sensory axonal neuropathy (AMSAN)</td>
<td>GM1 and GD1a</td>
</tr>
<tr>
<td>Ophthalmoplegia with ataxia and areflexia. Reduced or absent SNAPs without slowing of sensory conduction velocities</td>
<td>Miller Fisher syndrome</td>
<td>GQ1b (in 90%) and GT1a</td>
</tr>
<tr>
<td>Bickerstaff encephalitis</td>
<td>Overlap with Miller Fisher syndrome</td>
<td>GQ1b</td>
</tr>
<tr>
<td>Pharyngeal-cervical-brachial weakness</td>
<td>-</td>
<td>GT1a, GQ1b</td>
</tr>
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characterised by spontaneous motor unit discharges in the form of doublets, triplets and multiplet bursts (Figure 2). Isaac’s syndrome is acquired immune mediated neuromyotonia associated with an antibody against presynaptic voltage gated potassium channels (VGKC). Autonomic system dysfunction, limbic encephalopathy and neuromyotonia together constitute Morvan’s syndrome. Recent reports have described the association of thyromma, small cell lung carcinoma and autoimmune thyroiditis with these syndromes.

Thus, the breadth and ambit of autoimmune neurological disorders is increasing day by day. A syndromic approach enables the neurophysiologist to consider investigating for the appropriate autoimmune/paraneoplastic disorder, and thereby administer directed immunomodulatory therapy.

References