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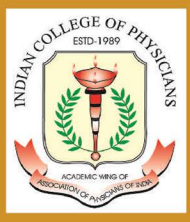

Monograph

Immune-mediated Neurological Disorders

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CHAPTER

Anti-neural Antibodies and the Disease Associations

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INTRODUCTION

Neural antibodies are defined as antibodies that are targeted against neural antigens and produce neuronal injury due to T-cell mediated or antibody-mediated mechanisms. Neural antibodies are found to be associated with both physiological and pathological conditions. Pathologically, it can occur in both malignant and nonmalignant conditions. Initially in 1960s, immune-mediated mechanism was found to contribute to the pathogenesis of disease. Later in 1980s, by advent of immunohistochemical staining, antibodies were identified and these were related to neuronal cell and which in turn was associated with tumor. Detection of these autoantibodies helps in diagnosis of the disease and its further management. These antibodies are detected even before the appearance of tumor. In this chapter, we briefly describe the classification and pathogenesis of neuronal antibodies and its disease association.

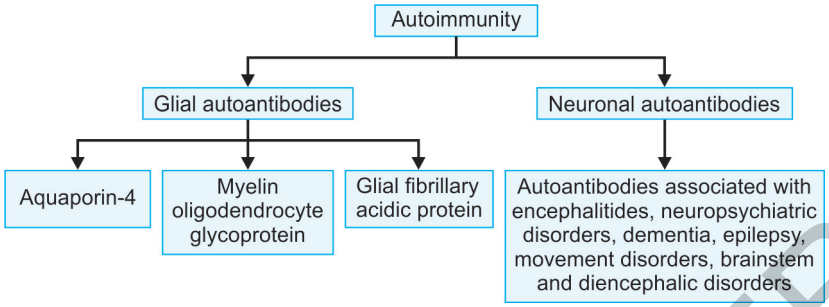
CLASSIFICATION

Classification of autoantibodies is based on:

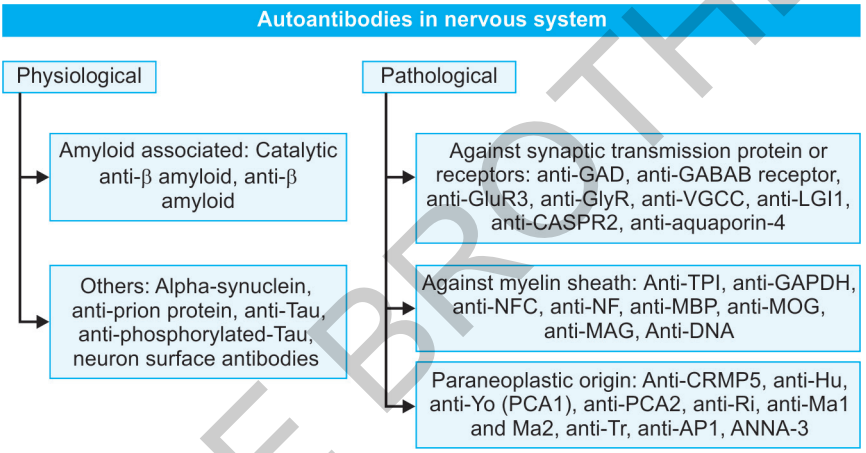
- Autoimmunity in nervous system
- Physiological and pathological origin
- Antigenic target location
- Association with malignancies and nonmalignancies.

Autoimmunity in Nervous System

Autoimmunity is defined as development of an immune response against one's own cells and tissues due to either failure of recognition of own cells or upregulation of expression of body's own cell. Autoimmunity in nervous system is classified on the basis of glial and neuronal autoimmunity (Flowchart 1). The advent of glial autoimmunity in pathogenesis of disease resulted in new treatment strategies in nervous system. For example, discovery of aquaporin-4 (AQP4) antibodies in pathogenesis of neuromyelitis optica (NMO) spectrum disorders paved the way for differentiating it from multiple sclerosis in pathogenesis, diagnosis, management, and predicting the outcome. The neuronal autoimmunity results in neuronal loss and dysfunction which results in encephalitis, dementia, and seizures.



FLOWCHART 1: Autoimmunity in nervous system.



GAD, glutamic acid decarboxylase; GABA, gamma amino butyric acid; LGI1, leucine-rich glioma-inactivated 1; CASPR2, contactin-associated protein-like 2; TPI, triosephosphatisomerase; GAPDH, glyceraldehyde-3-phosphatedehydragenase; NFC, neurofascin; NF, neurofilament; MBP, myelin basic protein; MOG, myelin oligodendrocyte glycoprotein; MAG, myelin associated glycoprotein; DNA, deoxyribonucleic acid; CRMP5, collapsin response mediator protein 5; PCA, purkinje cell cytoplasmic antibody; AP1, Activator protein 1; ANNA-3, anti-neuronal nuclear antibodies-3.

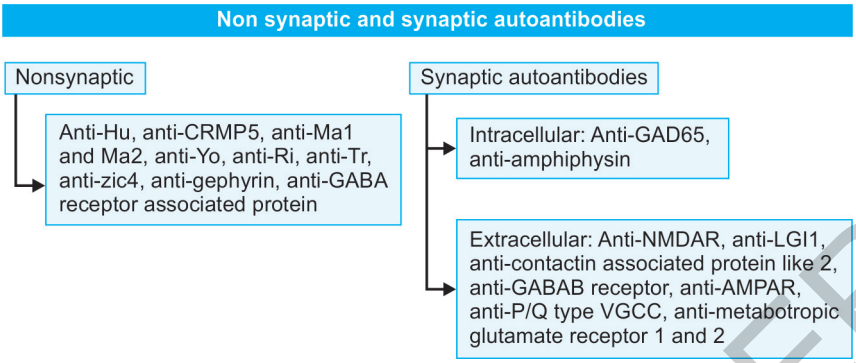
FLOWCHART 2: Classification of autoantibodies based on physiological and pathological origin.

Physiological and Pathological Origin

The autoantibodies are classified on the basis of physiological and pathological origin (Flowchart 2). The physiological (naturally occurring) autoantibodies are involved in brain homeostasis and help in clearing the protein aggregates. The pathological autoantibodies are mostly of paraneoplastic origin and some are associated with nonparaneoplastic origin.

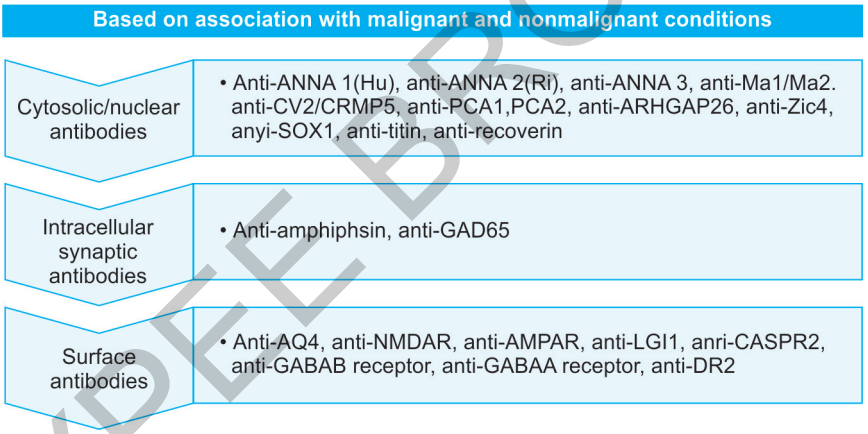
Antigenic Target Location

The autoantibodies are classified on the basis of targets at which they act and classified into synaptic and nonsynaptic (Flowchart 3). The synaptic autoantibodies act either intracellularly or extracellularly.



CRMP5, collapsin response mediator protein 5; GABA, gamma amino butyric acid; GAD65, glutamic acid decarboxylase 65kDa; NMDAR, N-methyl-d-aspartate receptor; LGI1, leucine-rich glioma-inactivated 1; AMPAR, α-amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid receptor; VGCC, voltage gated calcium channels; zic4, zinc finger protein 4.

FLOWCHART 3: Classification of autoantibodies based on antigenic target location—synaptic and nonsynaptic target antigens.



ANNA, anti-neuronal nuclear antibodies; CRMP5, collapsin response mediator protein 5; PCA, purkinje cell cytoplasmic antibody; ARHGAP26, Rho GTPase activating protein 26; GAD65, glutamic acid decarboxylase 65kDa; NMDAR, N-methyl-d-aspartate receptor; AQ4, aquaporin 4; AMPAR, α-amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid receptor; LGI1, leucine-rich glioma-inactivated 1; CASPR2, contactin-associated protein-like 2; GABA, gamma amino butyric acid.

FIG. 1: Classification of autoantibodies based on association with malignant and nonmalignant conditions.

Association with Malignancies and Nonmalignancies

Most of the autoantibodies described are of paraneoplastic origin and these antibodies act at different levels to produce various manifestations (Fig. 1). The antibodies acting on cell surface antigens may be paraneoplastic or most often nonparaneoplastic, whereas the antibodies against the nuclear or cytosolic antigens are mostly associated with malignant conditions. The neurological manifestations are described later in this chapter.

MECHANISM OF ANTIBODY-MEDIATED NEURONAL INJURY

Neural-specific antibody is often classically associated with a neurologic syndrome, the pathophysiology of which varies between diseases in situations like:

- Intracellular antigenic targets: The antibody is likely to be a marker of disease and is likely not to be pathogenic. In these cases, it is thought that the pathogenic agent is more likely the T-cell effector cell, which causes which cause irreversible injury due to T-cell mediated effects, and these are usually associated with malignancy and show poor response to treatment
- In contrast, antibody directed against cell surface antigens most often occurs in young individuals, may or may not be associated with cancer. They are directly pathogenic and produce distinct clinical syndromes which show good response to immunotherapy.

Pathogenesis of Neural Antibodies

Tumor-related Antibodies

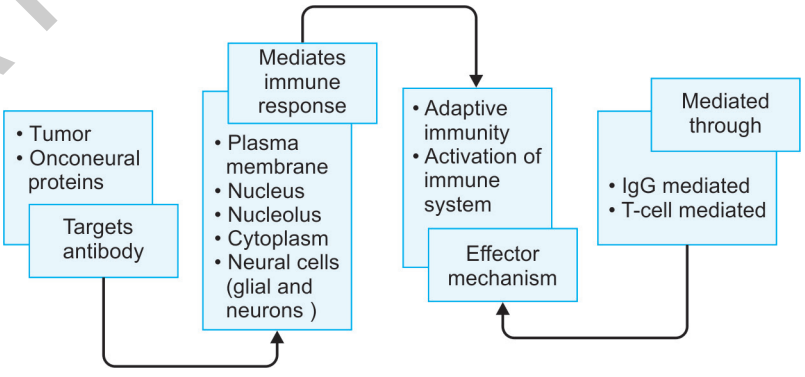
Neural injury is mainly due to tumor-mediated immune response which is initiated by onconeural proteins. These proteins are expressed in plasma membrane, nucleus, nucleolus, and cytoplasm of neural cells. Antigens in these sites are presented to adaptive immunity and results in activation of immune system leading to multiple effector mechanism [Immunoglobulin G (IgG) mediated or T-cell mediated] (Flowchart 4).

The Effector Mechanism

- Effector mechanism is different in the case of intracellular and cell surface antigens
- The mechanism of neuronal injury is mediated through T-cell in intracellular antigens, whereas it is antibody mediated with respect to cell surface antigens (Fig. 2).

Effector Mechanism for Cell Surface and Membrane Antigens

- Antibody targets the antigens on plasma cell membrane and acts as effectors of injury



FLOWCHART 4: Pathogenesis of neural antibodies.

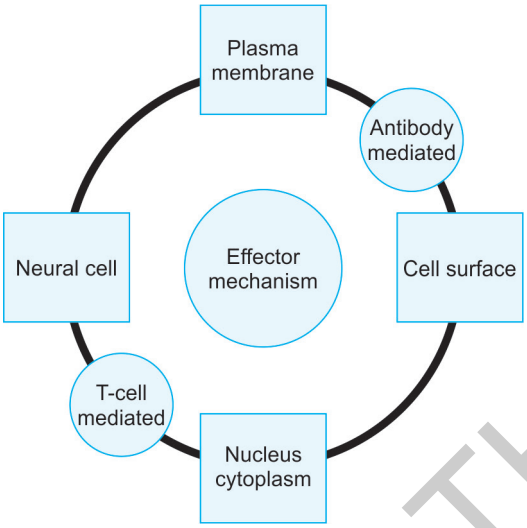


FIG. 2: Effector mechanism.

FIG. 3: Effector mechanism of intracellular antigens.

- Antibody targeting on neural cell membrane acts on various channels [voltage-gated potassium channel (VGKC), N-methyl-d-aspartate (NMDA), alpha-amino-3-hydroxy-5-methyl-4-isoxazole-propionic acid (AMPA), gamma amino butyric acid (GABA)-B, AQP4] which leads to cell dysfunction
- Alteration or modulation of cell surface antigen by the neural antibodies activates various channels and produces damage in different ways like:
  - Receptor agonist or antagonist effects
  - Activation of complement cascade
  - Activation of Fc receptor: Leading to antibody-dependent cell-mediated cytotoxicity
  - Antigen internalization (Antigenic modulation): Alters the antigen density on the cell surface.

Effector Mechanism for Intracellular Antigens

Intracellular antigenic proteins (neural or cytoplasmic) undergo proteasomal degradation into peptides which are exposed to immune system through upregulation of major histocompatibility complex class I. These are then recognized by cytotoxic T-cells in a proinflammatory cytokine environment leading to T-cell activation and neural injury. Effector mechanism of injury is mainly mediated through peptide-specific cytotoxic T-cells (Fig. 3).

ANTINEURONAL ANTIBODIES AND ITS DISEASE ASSOCIATION

Classically, antineuronal antibodies are divided into two groups based on the target antigen.

- Nonsynaptic antibodies which include intracellular nuclear and cytoplasmic antibodies
- Synaptic antibodies which again divide into intracellular synaptic antibodies and extracellular or surface antibodies.

Nuclear and Cytoplasmic Antibodies

Antibodies against nuclear and cytoplasmic target antigen are nonpathogenic. They directly do not produce lethal affect. Presence of antibodies in cerebrospinal fluid (CSF) or serum acts as a marker for cancer. Possible mechanism by which these antibodies produce disorders is T-cell mediated response. For example, presence of Hu antibodies in small cell lung cancer. Expression of Hu is triggered by T-cell mediated autoimmune response.
Various nonsynaptic antibodies and its associated syndromes are described in Table 1.

Intracellular Synaptic Antibodies

Intracellular synaptic antibodies are glutamic acid decarboxylase 65(GAD65) and amphiphysin. Glutamic acid decarboxylase 65 is concentrated in presynaptic terminals. Amphiphysins are proteins belonging to Bin-Amphiphysin-Rvs167 superfamily, which are important for recycling of vesicles in synaptic terminal through endocytosis mediated by clathrin. The pathological effects of GAD65 are through both antibody-mediated and T-cell mediated mechanisms (Table 2).

Cell-surface and Synaptic Antigens

Recently, large number of synaptic or cell surface antibodies are identified. The pathological effect of these antibodies is similar to disruption in the function of target antigen. Various cell surface and synaptic antibodies and their association with various syndromes are shown in Table 3.

CLINICAL PHENOTYPE-BASED APPROACH TO AUTOIMMUNE ANTIBODIES

Anti-neural antibodies produce various syndromes based on the target of action. It may be predominately peripheral or central syndromes. Based on clinical phenotype of various syndromes, they are divided into paraneoplastic syndromes or classic syndromes and idiopathic or nonclassic syndromes. Paraneoplastic syndromes are almost associated with malignancy and idiopathic syndromes do not have any evidence for malignancy (Table 4).

CLINICAL PRESENTATIONS OF ANTINEURAL ANTIBODIES WITH CENTRAL NERVOUS SYSTEM INVOLVEMENT

These are divided into:

- Autoimmune encephalitis
- Autoimmune dementia and neuropsychiatric disorders

TABLE 1: Nonsynaptic antibodies and associated disorders

Antibody	Antigen and mechanism	Associated tumor	Clinical constellation
Anti-Hu	• Hu proteins (HuD, HuC and Hel-N1, N2 • Neuronal RNA handling T-cell mediated	Small cell lung cancer	Sensory neuropathy, limbic encephalitis, cerebellitis and brainstem encephalitis
Anti-Yo	• Yo proteins (CDR1 in Purkinje cells)t • CDR2 in cell cycle regulation and transcriptional regulation • Possibly T-cell mediated	Breast and gynecological malignancy	Paraneoplastic cerebellar degeneration
Anti-Ri	• Ri proteins (Nova 1 and Nova 2) • Nova 1 RNA binding protein • Antibodies inhibit binding of Nova 1 to RNA	Breast cancer	Paraneoplastic cerebellar degeneration, opsoclonus-myoclonus syndrome, encephalitis, and myelitis
Anti-CRMP5	• CRMP5 • Neurogenesis and its regulation • T-cell mediated	Small cell lung cancer, thymoma	Polyneuropathy, limbic encephalitis, cerebellar degeneration and uveoretinal syndrome
Anti-Ma	• Ma proteins (Ma1 and Ma2) • Ma1- apoptosis regulation • T-cell mediated	• Ma1–skin, lung, renal and gastrointestinal cancer • Ma2–germ cell tumors	Limbic encephalitis, cerebellitis, brainstem encephalitis and neuropathy
Anti-Tr	Tr proteins in Purkinje cells	Hodgkin lymphoma	Paraneoplastic cerebellar degeneration
Anti-gephyrin	• Gephyrin • Involved in GABAergic transmission	Mediastinal carcinoma	Stiff person syndrome
Anti-ZIC4	• Zinc finger protein • Mostly nonpathogenic	Small cell lung cancer	Paraneoplastic cerebellar degeneration

CDR, complementarity determining region; RNA, ribonucleic acid; CRMP5, collapsin response mediator protein 5; GABA, gamma amino butyric acid; ZIC4, zinc finger protein 4.

- Autoimmune epilepsy
- Diencephalic and brainstem disorders
- Immune-mediated movement disorders
- Autoimmune myelopathies
- Aquaporin-4 autoimmunity
- Myelin oligodendrocyte glycoprotein (MOG) autoimmunity
- Glial fibrillary acidic protein (GFAP) autoimmunity
- Stiff person syndrome
- Progressive encephalomyelitis with rigidity and myoclonus
- Autoimmune cerebellopathies.

TABLE 2: Intracellular synaptic antibodies and its associated disorders

Antibody	Antigen and mechanism	Associated tumor	Clinical constellation
Anti-amphiphysin	• Amphiphysin-synaptic vesicles recycling • Pathogenic	Breast cancer	Stiff person syndrome
Anti-GAD65	• Glutamic acid decarboxylase • Important for GABA synthesis • T cell mediated and antibody mediated	Rarely neuroendocrine tumors	Cerebellitis, stiff person syndrome

GAD65, glutamic acid decarboxylase; GABA, gamma amino butyric acid.

TABLE 3: Cell surface antigens and its associated disorders

Antibody	Antigen and mechanism	Associated tumor	Clinical constellation
Anti-NMDAR	• NMDAR NR1 subunit is the primary target • Important for learning and memory • Antibodies cross link with NMDAR and internalization of receptors	Ovarian teratoma	Limbic encephalitis, psychiatric symptoms, catatonia, autonomic dysfunction
Anti-GABAB	• GABA B receptor • Primarily inhibits synaptic transmission	Small cell lung cancer	Limbic encephalitis, refractory seizures
Anti-AMPA	• AMPA receptor • Important for learning and memory	Breast and lung cancer, thymoma	Limbic encephalitis
Anti-LGI 1	• Leucine-rich glioma inactivated protein 1 • Secreted protein • Crucial role in regulation of presynaptic VGKC Kv1	None	Hyponatremia, limbic encephalitis, seizures or myoclonus
Anti-CASPR2	• Contactin associated protein 2 • Crucial role on organization of VGKC Kv1 channels	Thymoma	Limbic encephalitis, neuromyotonia
Anti-VGCC	• Voltage-gated calcium channels P/Q type • Important for presynaptic calcium influx • Pathogenic blocking of calcium influx	Small cell lung cancer	Lambert–Eaton myasthenia syndrome
Anti-metabotropic glutamate receptor	• Metabotropic glutamate receptor 1–important for cerebellar function	Hodgkin lymphoma	Cerebellitis
	• Metabotropic glutamate receptor 5–important for hippocampal function	Hodgkin lymphoma	Ophelia syndrome

NMDA, N-methyl-d-aspartate receptor; GABA, gamma amino butyric acid; AMPA, alpha-amino-3-hydroxy-5-methyl-4- isoxazole-propionic acid; LGI1, leucine-rich glioma-inactivated 1; CASPR2, contactin-associated protein-like 2; VGKC, voltage-gated potassium channel.

TABLE 4: Clinical phenotype-based approach

Site	Paraneoplastic syndrome	Idiopathic syndrome
Central nervous system	• Encephalomyelitis • Limbic encephalitis • Paraneoplastic cerebellar degeneration • Opsoclonus-myoclonus syndrome	• Brainstem encephalitis • Stiff person syndrome • Necrotizing myelopathy • Motor neuron disease
Dorsal root ganglia or peripheral nerves	• Subacute sensory neuronopathy • Gastrointestinal paresis or pseudo-obstruction	• Acute sensorimotor neuropathy (Guillain–Barre syndrome, plexitis) • Subacute and chronic sensorimotor neuropathies • Neuropathy of plasma cell dyscrasias and lymphoma • Pure autonomic neuropathy • Vasculitic neuropathies
Muscle	Dermatomyositis	• Acute necrotizing myopathy • Polymyositis
Neuromuscular junction	Lambert–Eaton myasthenia syndrome	• Myasthenia gravis • Acquired neuromyotonia
Eye and retina	• Cancer associated retinopathy • Melanoma associated retinopathy	Optic neuritis

Autoimmune Encephalitis

The presentation is usually a subacute onset of an encephalitic syndrome with altered sensorium, seizures, psychiatric disturbances, and movement disorders. Syndromes due to autoimmune encephalitis and due to autoimmune dementia and neuropsychiatric disorders are combined together because of frequent overlap (Table 5).

Autoimmune Epilepsy

Autoimmune epilepsy is suspected when the patient has any one of the following:

- Status epilepticus which is new onset
- Refractory status epilepticus
- Rapid cognitive decline
- Early age of onset (Table 6).

Autoimmune Myelopathy

Based on the course of the disorder, autoimmune myelopathies are divided into:

- Acute or subacute onset of motor, sensory, or autonomic spinal cord dysfunction
- Insidious onset and progressive course
- Motor neuron disease-like presentation (Table 7).

TABLE 5: Antibodies associated with autoimmune encephalitis

Syndrome	Antibodies	Associated cancer
Anti-NMDA receptor encephalitis	NMDA receptor	Ovarian teratoma
Limbic encephalitis	• AMPA receptor • GABAB receptor • LGI1 • CASPR2 • Hu (ANNA-1) • Ma2 • GAD	• Thymoma, small cell lung carcinoma • Small cell lung carcinoma • Thymoma • Thymoma • Small cell lung carcinoma • Testicular seminoma • Thymoma, small cell lung carcinoma
Encephalitis	• GABAA • mGLuR5 • DPPX	• Thymoma • Hodgkin's lymphoma • Lymphoma
Acute disseminated encephalomyelitis	MOG	–
Basal ganglia encephalitis	Dopamine 2 receptor	–
Bickerstaff's encephalitis	GQ1b	–
NMO spectrum disorder	Aquaporin 4	–

NMDA, N-methyl-d-aspartate; GABA, gamma amino butyric acid; AMPA, alpha-amino-3-hydroxy-5-methyl-4-isoxazole-propionic acid; MOG, myelin oligodendrocyte glycoprotein; LGI1, leucine-rich glioma-inactivated 1; CASPR2, contactin-associated protein-like 2; GAD, glutamic acid decarboxylase; ANNA, anti-neuronal nuclear antibodies; DPPX, dipeptidyl-peptidase-like protein-6; GQ1b, Ganglioside Q1b.

Autoimmune Neuropathy

Various phenotypic presentations of autoimmune neuropathy are:

- Sensory neuronopathy, most common
- Autonomic enteric neuropathy
- Demyelinating neuropathy
- Motor neuropathy very rare (Table 8).

Autoimmune Cerebellopathies

Cerebellar Purkinje cell proteins are target antigen for various antineural antibodies (Table 9).

Autoimmune Movement Disorder

They frequently occur in adults. Complete range of movement disorder phenotype is associated with autoimmune movement disorder. It may mimic a neurodegenerative disease. Antibodies associated with autoimmune movement disorder are shown in Table 10.

Autoimmune Neuromuscular Disorders

Autoimmune disorders of neuromuscular junction (NMJ) cause severe neurological impairment. The mechanism of NMJ failure could be destruction of normal structures

TABLE 6: Antibodies associated with autoimmune epilepsy

Various group	Syndromes	Antibodies
Paraneoplastic limbic encephalitis	Limbic encephalitis	Anti-Ma, mGluR5, CRMP5, amphiphysin, VGCC
Antibodies against VGKC channels	Limbic encephalitis	LGI1, CASPR2
NMDA encephalitis	Encephalitis	NMDAR
Rasmussen encephalitis	Encephalitis	GluR3
Other neuronal surface antigens	Limbic encephalitis	GABAA, GABAB, TPO, TG, SOX1
De novo febrile illness	• NORSE (new onset refractory status epilepticus) • FIRES (febrile infection related epilepsy syndrome) • AERRPS (acute encephalitis with refractory repetitive partial seizures)	None
Other autoimmune disorders	• ADEM • Nonconvulsive status • Epilepsia partialis continua	ADEM-anti MOG antibodies
Systemic autoimmune disorder	• SREAT (steroid responsive encephalopathy with autoimmune thyroiditis) • SLE	None

VGCC, voltage-gated calcium channel; SLE, systemic lupus erythematosus; NMDA, N-methyl-d-aspartate; GABA, gamma amino butyric acid; LGI1, leucine-rich glioma-inactivated 1; ADEM, acute disseminated encephalomyelitis; CASPR2, contactin-associated protein-like 2; VGKC, voltage-gated potassium channel; CRMP5, collapsin response mediator protein 5; TPO, thyroid peroxidase antibody; TG, Thyroglobulin; MOG, myelin oligodendrocyte glycoprotein.

which are responsible for function and transmission of signal or dysfunctional activity of same due to targeted mutation as seen in congenital myasthenic syndromes. Autoimmune NMJ disorders are classified as presynaptic and postsynaptic. Presynaptic antibodies are directed against voltage gated calcium channel in presynaptic terminals, thereby interfering with the presynaptic calcium influx required for acetylcholine release. In the paraneoplastic setting, 40% of cases are associated with small cell carcinoma of lung (SCLC). Around 3% patients with SCLC have Lambert–Eaton myasthenic syndrome (LEMS) that usually occurs in elderly. Other malignant conditions are Hodgkin's lymphoma, malignant thymoma and atypical carcinoid syndromes. Anti-SOX 1 is another presynaptic antibody implicated in paraneoplastic LEMS. In postsynaptic region, the antibodies are anti-MuSK, low density lipoprotein receptor-related protein family of transmembrane protein (LRP4), anti-rapsyn antibody, antibody targeted against non-AChR skeletal muscle proteins like anti-titin, anti-ryanodine, antibody against non-AChR ion channels like voltage-gated Kv1.4 is implicated.

Aquaporin-4 Autoimmunity

Aquaporin-4, a water channel protein, primarily located in astrocytes, is the target antigen in NMO spectrum disorder. Usually, NMO-IgG is not associated with any cancer. AQP4

TABLE 7: Common autoimmune myelopathies and its associated antibodies

Disease	Antibody	Cancer association	Course	Presentation
Multiple sclerosis	–	–	Relapsing	Subacute asymmetric
NMO	Aquaporin 4	–	Relapsing	Subacute symmetric
ADEM	MOG	–	Monophasic	Subacute multifocal with encephalitis
Paraneoplastic myelopathy	CRMP5 amphiphysin	Breast and lung carcinoma	Chronic progressive	Insidious
Autoimmune/ paraneoplastic motor neuron disease	Variable	Breast and lung carcinoma, lymphoma	Chronic progressive	• Mixed upper and lower motor neuron • ALS or PLS
Stiff person syndrome	Anti-GAD65 amphiphysin	Small cell lung cancer, thymoma	Chronic progressive	–
Progressive encephalomyelitis with rigidity and myoclonus	Anti-glycine receptor antibody	–	Subacute progressive	–

GAD, glutamic acid decarboxylase; NMO, neuromyelitis optica; MOG, myelin oligodendrocyte glycoprotein; ALS, amyotrophic lateral sclerosis; PLS, primary lateral sclerosis; ADEM, acute disseminated encephalomyelitis; CRMP5, collapsin response mediator protein 5.

is present in two major isoforms produced by alternative splicing: a relatively long (M1) isoform with translation initiation at Met-1, and a shorter (M23) isoform with translation initiation at Met-23. Aquaporin-4 monomers assemble as tetramers. The tetramers uniquely further aggregate in cell plasma membranes to form supramolecular assembles called orthogonal arrays of particles (OAPs) which were originally visualized in membranes by freeze-fracture electron microscopy. Aquaporin-4 is most strongly expressed in the central nervous system (CNS), but is also present in epithelial cells in the kidney (collecting duct), the stomach (parietal cells), airways, glands, and skeletal muscle. Aquaporin-4 is expressed in astrocytes in the brain, spinal cord, and optic nerve, and is particularly concentrated at pial and ependymal surfaces in contact with the CSF. At the cell level, AQP4 expression is polarized to foot processes of astrocytes in contact with blood vessels. Aquaporin-4 is also expressed in so-called supportive cells, similar to astrocytes in sensory organs such as Muller cells in the retina. Pathological changes associated with NMO mostly occur in the spinal cord and optic nerve, and to a lesser extent in the brain, with a notable absence of abnormalities in peripheral AQP4-expressing tissues.

Myelin Oligodendrocyte Glycoprotein Autoimmunity

Target protein in MOG autoimmunity is MOG belonging to immunoglobulin superfamily. It is expressed exclusively on the outer surface of myelin sheath and plasma membrane of the oligodendrocytes. Myelin oligodendrocyte glycoprotein is the most important surface

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