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Indian Academy of Neurology

Advances in Movement Disorders

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CHAPTER 11

Diagnosis and Management of Autoimmune Movement Disorders

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ABSTRACT

Neuroimmunology is a rapidly evolving field. The discovery of newer antibodies and syndromes continuously expands the clinical spectrum and our understanding of the pathophysiology and treatment of autoimmune neurological disorders. Movement disorders are common in autoantibody-associated neurological diseases. This is a category of potentially treatable conditions, and differentiation from metabolic, infectious, or neurodegenerative disorders, which they mimic, is vital for this reason. Acquired movement disorders resulting from immune-mediated mechanisms require early recognition due to their treatment implications. The autoantibodies behave differently in their response to therapy and association with malignancy, based on their antigenic targets being extracellular, synaptic intracellular, or cytoplasmic. Awareness regarding distinct clinical features characteristic of specific autoimmune movement disorders (AMDs) is essential for clinicians to enable precise antibody testing and prompt treatment initiation. This review classifies AMDs as primary and secondary and describes the antibodies associated with primary AMDs. The salient features of major AMDs, phenomenology-based approach, and decision-making protocols based on the presence and type of autoantibodies are elaborated further, thereby providing a practical guide for evaluating and managing AMDs.

Keywords: Movement disorders, Autoimmune, Paraneoplastic, Autoantibodies.

INTRODUCTION

Autoimmune movement disorders (AMDs) are an evolving and heterogeneous group of conditions, with an increasing number of syndromes and autoantibodies being discovered. Movement disorders are probably the most noticeable symptoms in neuroimmunology, bringing the patient to the physician. Autoimmune causes are reported in up to 42% of children with acute movement disorders.[1] AMDs often coexist with limbic encephalitis, epilepsy, or peripheral neuropathy. Early diagnosis is crucial because some antibodies are associated with occult neoplasia, which can be potentially treatable. However, many patients are diagnosed late or often misdiagnosed. Although certain movement disorders can form classic syndromes pointing toward specific autoantibodies, clinical diagnosis is often challenging because of the overlapping presentations and often undetectable antibodies.

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CLASSIFICATION OF AUTOIMMUNE MOVEMENT DISORDERS

Clinical conditions manifesting as movement disorders (hypo- or hyperkinetic) and resulting from an autoimmune etiology are termed AMDs.[2] They can be arbitrarily classified into two groups:

1. *Primary AMDs:* These are caused by autoantibodies, usually triggered by infections or neoplasms and primarily targeting the central nervous system (CNS), including the nodes of the neural circuits concerned with motor control. The antigenic targets could be extracellular, synaptic intracellular, or cytoplasmic. This group includes various autoimmune encephalitis (AIE) syndromes and paraneoplastic encephalitis manifesting as movement disorders.[3,4]
2. *Secondary AMD:* This group is constituted by systemic autoimmune conditions causing movement disorders secondary to nervous system affliction. These are usually associated with prominent extraneurological manifestations. Immune-mediated primary CNS demyelinating disorders like multiple sclerosis (MS) sometimes cause movement disorders secondary to damage to basal ganglia or cerebellar circuits and these also could be considered as secondary AMDs.[5]

CLASSIFICATION OF AUTOANTIBODIES

As discussed above, the autoantibodies causing AMDs can be targeted toward extracellular, synaptic intracellular, or cytoplasmic antigens. Characterization of autoantibodies in primary AMDs based on immunological mechanisms targeting different cellular components has treatment implications.[2,6,7] Autoantibodies against the neuronal cell surface receptors cause receptor dysfunction, which is usually reversible, leading to dysregulation of downstream mechanisms and manifesting as hyperkinetic movement disorders, seizures, or cognitive decline. They exert pathogenicity through antibody-mediated mechanisms such as antigen internalization, direct agonist or antagonist effects on receptors and activation of the complement cascade, or through cell-mediated cytotoxicity leading to neuronal damage.[1] These disorders have, in general, a favorable response to immunotherapy and when they occur in a paraneoplastic setting, treatment of the underlying neoplasm.[2,8]

The second group of autoantibodies target antigens localized to the presynaptic intracellular region and interferes with the release of inhibitory neurotransmitters. These commonly manifest as ataxia and Stiff–person phenotype. They have an intermediate response to immunotherapy.[2] The third group is composed of onconeural antibodies targeting the cytoplasmic and nuclear antigens, highly associated with malignancies and presenting as paraneoplastic syndromes of the varied clinical picture. Such antibodies directed against intracellular components are useful as biomarkers of the disease and aid diagnosis but are usually not causative because there is no opportunity for the antibodies to bind to the intracellular targets. The associated diseases are thought to be mediated by autoreactive T cells and this group is poorly responsive to immunotherapy.[8,9] Examples of AMDs under each category of autoantibodies are mentioned in **Table 1**.

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TABLE 1: Salient features of antibodies directed against different cell targets.

Autoantibody target	Neuronal cell surface receptors (B cell-mediated)	Intracellular synaptic proteins	Cytoplasmic and nuclear antigens (T cell-mediated)
Usual clinical features	Seizures, cognitive dysfunction, orolingual dyskinesias, ataxia, and parkinsonism	Ataxia, Stiff-person syndrome	Ataxia, limbic encephalitis
Prototype antigen target examples	NMDARE, LGI1, CASPR2, DPPX, Dopamine-2-R, IgLON5, GABAAR, GABABR, VGCC, mGluR1, mGluR5, Neurexin-3α, and AQP4	GAD, amphiphysin, GlyR, Gephyrin, and GABARAP	Hu, CV2/CRMP5, Yo, Ma, Ri, Zic4, PCA2, Sox1, GFAP
Association with malignancy	Low and variable	Moderate	High
Response to immunotherapy	Favorable	Moderate	Poor

(AQP4: aquaporin-4; CASPR2: contactin-associated protein-like 2; CV2/CRMP5: collapsin response-mediator protein 5; DPPX: dipeptidylpeptidase-like protein-6; GABAAR: γ-aminobutyric acid A receptor; GABABR: γ-aminobutyric acid B receptor; GAD: glutamic acid decarboxylase; GFAP: glial fibrillary acidic protein; GlyR: glycine receptor; IgLON5: immunoglobulin-like cell adhesion molecule 5; LGI1: leucine-rich glioma-inactivated 1; mGLuR1: metabotropic glutamate receptor type 1; mGLuR5: metabotropic glutamate receptor type 5; NMDARE: N-methyl-D-aspartate receptor encephalitis; PCA2: Purkinje cell antibody 2; SOX1: Sry-like high mobility group box 1; VGCC: voltage-gated calcium channel; Zic4: zinc finger domain of the intracellular transcription factor)

AUTOIMMUNE MOVEMENT DISORDERS WITH WELL-CHARACTERIZED ANTIBODIES AND CLINICAL PHENOTYPES

The characteristic features of some important AMDs are mentioned below. A description of different autoantibody-mediated syndromes is also summarized in **Table 2**.[10-42]

Anti-N-methyl-D-aspartate Receptor Encephalitis

N-methyl-D-aspartate receptor encephalitis (NMDARE) was identified to be more than four times as frequent as viral encephalitis in the California Encephalitis Project and was considered the single most common cause of encephalitis in individuals under the age of 30 years.[10] NMDARE exhibits a myriad of movement disorders of which orolingual, facial, and lingual dyskinesias are the most characteristic **(Table 2)**. Isolated movement disorder presentation is rare; patients mostly present with subacute onset psychiatric or cognitive dysfunction, speech disturbances including mutism, seizures, autonomic dysfunction, central hypoventilation, hyperkinetic movement disorders, and altered sensorium which form the six major groups of symptoms.[3,8] They often exhibit an age-dependent clinical presentation.[7,11] Children are more likely to develop movement disorders and seizures, which are generally refractory to symptomatic therapy and improve gradually with recovery from the disease following immunotherapy,[1] while adults mostly have neuropsychiatric and behavioral disturbances. Prodromal fever and headache are reported by many patients. The disease is mostly idiopathic; sometimes, it can be triggered by either malignancy (particularly, ovarian teratoma in young women) or infection like herpes simplex encephalitis.[12] The diagnostic criteria offer two levels of certainty. Definite NMDARE requires the presence of cerebrospinal fluid (CSF) antibodies against the glycine

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TABLE 2: Autoantibodies, associated autoimmune movement disorders (AMDs), and other clinical features.

Antigen target	Demographics	Movement disorders	Other clinical features	Tumor association	Ancillary investigations
NMDARE[1,2,8,30]	Young women (15–40 years) and children	Orofacial and lingual dyskinesias, dystonia, stereotypies, chorea, myorhythmia, and cerebellar ataxia	Altered sensorium, seizures, catatonia, speech dysfunction, memory decline, central hypoventilation, and dysautonomia	Ovarian teratoma, lung, and testicular carcinoma	Extreme delta brush in EEG. T2/FLAIR signal hyperintensities in the hippocampus, temporal cortex, frontal cortex, and brainstem. Anti-NMDARE antibodies demonstrated in CSF have higher sensitivity than in serum
LGI-1[1,2,31]	More common in males; typical age—sixth and seventh decades	FBDS, chorea, myoclonus, dystonia, and parkinsonism	Amnesia, seizures, personality changes, psychosis, sleep disorders, Morvan syndrome, and neuropathic pain	Thymoma	Hyponatremia in 70% of patients. Episodic bradycardia in ECG. Serological studies are more sensitive than CSF for *LGI1* antibodies. Hyperintensities in T2-weighted MR images in the mesial temporal lobe
CAPSR2[1,2,30,37]	Much more common in males (sex ratio 8:1). Typical age—fifth and sixth decades	Ataxia, chorea, orthostatic myoclonus, trunk flexion superficially resembling psychogenic propriospinal myoclonus, parkinsonism	Morvan syndrome, neuropathic pain, limbic encephalitis, and seizures	Thymoma, prostate and lung cancer, and melanoma	Nonspecific inflammatory changes in CSF and MRI. Neuromyotonia, fasciculations, and myokymic discharges in EMG. Serum assessments are highly sensitive for *CASPR2* antibodies
DPPX[1,37]	More common in males in fifth and sixth decades	Hyperekplexia, tremor, myoclonus, SPS, PERM, ataxia, and PLMS	Prolonged diarrhea, weight loss, seizures, psychiatric symptoms, dysautonomia, and intractable pruritus	B-cell lymphoma	Normal MRI. Anti-DPPX detectable in both serum and CSF

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Antigen target	Demographics	Movement disorders	Other clinical features	Tumor association	Ancillary investigations
GABAAR[1,30,38]	Young males, median age of 41 years, range from 17 to 73 years	Dystonic tongue movements, chorea, opsoclonus, ataxia, and orofacial dyskinesias	Seizures (most prominent), status epilepticus, and encephalopathy	Hodgkin's lymphoma	MRI—Multifocal T2-FLAIR cortical-subcortical hyperintensities involving cingulate, temporal (95%), and frontal (65%) regions, basal ganglia, cerebellum, and brainstem
GABABR[1,39]	Equal gender distribution, Usual age: 40–50 years	Ataxia, chorea, and opsoclonus	Refractory status epilepticus, encephalopathy,and limbic encephalitis syndrome	SCLC	• Brainstem, basal ganglia, and mesial temporal lobe hyperintensities in MRI • Concurrent GAD antibody positivity can occur
D2R[1,40]	Equal gender distribution. Usually affects children; Median age: 10 years	Basal ganglia encephalitis manifesting as generalized or hemidystonia, parkinsonism, oculogyric crisis, chorea and tics	Psychiatric symptoms, seizures, ocular flutter, and encephalopathy	None	T2-FLAIR hyperintensities within the basal ganglia, in MRI
KLH11[37]	Usually affect males. Age range: 9–72 years	Ataxia and OMAS	Hearing loss, cognitive decline, limbic encephalitis syndrome, and psychosis	Testicular seminoma, ovarian teratoma	Nonspecific inflammatory changes in CSF and MRI
GAD[2]	Middle-aged females	Ataxia, palatal myoclonus, and PERM	SPS, episodic vertigo, limbic encephalitis, seizures. Can be comorbid with type 1 diabetes and thyroiditis	SCLC and thymoma	CSF anti-GAD antibodies are usually positive. EMG shows continuous agonist and antagonist motor activity, typically in axial muscles. Epileptiform discharges in EEG. Normal or showing bilateral T2-FLAIR mesial temporal hyperintensities in MRI

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Antigen target	Demographics	Movement disorders	Other clinical features	Tumor association	Ancillary investigations
GlyR[30]	No gender predilection, wide age range of 1–75 years	SPS and PERM	Epilepsy, brainstem, autonomic, and long-tract signs	Thymoma, SCLC, and breast cancer	Nonspecific inflammatory changes in CSF and MRI
Amphiphysin[30]	Females, median age 52 years	SPS and ataxia	Sensory neuronopathy, myelopathy and limbic encephalitis syndrome	Breast and lung cancer	Nonspecific inflammatory changes in CSF and MRI
GFAP astrocytopathy[30,41]	No gender predilection, median age: 42 years	Tremor and ataxia	Meningoencephalitis, myelitis, headache, papilledema and subacute encephalopathy	Prostate and gastrointestinal adenocarcinoma, melanoma, myeloma	Characteristic MRI findings—radial, linear periventricular, or cerebellar gadolinium enhancement
Hu[30]	Middle-aged and older adult males	Chorea, opsoclonus-myoclonus, and pseudoathetosis	Sensory neuronopathy, limbic encephalitis, rhombencephalitis, gastrointestinal pseudo-obstruction, sensorineural hearing loss	Small cell lung cancer	Anti-Hu antibodies in both serum and CSF. Nonspecific inflammatory changes in CSF and MRI. Epileptiform discharges in EEG, FDG-PET shows extensive bilateral mesial temporal hypermetabolism
Ri[30]	More in women aged more than 45 years	Cranio-cervical dystonia (jaw closing or opening dystonia), cerebellar ataxia	Oculomotor disturbances, encephalopathy, and SPS	Breast cancer	Cerebellar atrophy. Nonspecific inflammatory changes in CSF and MRI
CV2/CRMP5[28,30,42]	No gender predilection, 60–70 years	Chorea, dystonia, and ataxia	Limbic encephalitis, optic neuritis, uveitis, myelitis, sensory neuronopathy, anosmia, and ageusia	SCLC, Thymoma, NHL, and breast cancer	Nonspecific inflammatory changes in CSF and MRI
Ma[21,22]	Young males 30–40 years; elderly females aged 60–70 years	Parkinsonism, PSP-like phenotype, cataplexy, and cerebellar ataxia	Weight gain, limbic, diencephalic, and brainstem encephalitis, myelopathy, radiculo-plexopathy, and sleep disorders like RBD	Testicular malignancy, SCLC, and breast cancer	Typical MRI pattern with thalamic and hypothalamic T2 hyperintensities

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Antigen target	Demographics	Movement disorders	Other clinical features	Tumor association	Ancillary investigations
PDE10A[11,30]	No gender predilection, median age: 70 years	Chorea, dystonia, and ballismus	Encephalopathy	SCLC and renal adenocarcinoma	Nonspecific inflammatory changes in CSF and MRI, bilateral striatal lesions
IgLON5[16-20]	No gender predilection, Age: 40–70 years	Characteristic NREM parasomnia (finalistic movements), RBD, abdominal; dyskinesia, parkinsonism, ataxia, dystonia, chorea, myoclonus, and SPS	Prominent sleep dysfunction, OSA, bulbar dysfunction, motor neuron disease, supranuclear gaze palsy	None	PSG demonstrates OSA, complex non-REM parasomnia, and stridor during sleep. Anti-*IgLON5* detected in serum and CSF (IgG4 or IgG1). CSF antibodies more specific. Associated with human leukocyte markers HLA-DRB1*10:01 and HLADQB1*05:01. Neuropathology demonstrates accumulation of hyperphosphorylated tau, preferentially in the hypothalamus and brainstem tegmental nuclei
SEZ6L2[11]	No gender predilection, median age 62 years	Cerebellar ataxia and atypical parkinsonism	Cognitive impairment, dysarthria	None	Mostly normal CSF and MRI brain. Antibodies of IgG4 class predominantly
mGluR5[11,28]	Females, median age 30 years	Myoclonus, dystonia, orofacial dyskinesias, and postural tremors	Neuropsychiatric symptoms, Ophelia syndrome (encephalitis, memory deficits, and dreamy state)	SCLC and Hodgkin's lymphoma	Nonspecific inflammatory changes in CSF and MRI

(CASPR2: contactin-associated protein-like 2; CSF: cerebrospinal fluid; D2R: dopamine receptor type 2; DPPX: dipeptidylpeptidase-like protein-6; EEG: electroencephalogram; EMG: electromyogram; FBDS: faciobrachial dystonic seizures; FDG-PET: [^{18}F]Fluorodeoxyglucose positron emission tomography; FLAIR: fluid-attenuation inversion recovery; IgLON5: immunoglobulin-like cell adhesion molecule-5; GABAAR: γ-aminobutyric acid A receptor; GAD: glutamic acid decarboxylase; GFAP: glial fibrillary acidic protein; GlyR: glycine receptor; KLHL11: Kelch-like protein 11; LGI1: leucine-rich glioma-inactivated 1; MRI: magnetic resonance imaging; mGLuR5: metabotropic glutamate receptor type-5; NHL: non-Hodgkins lymphoma; NMDARE: N-methyl-D-aspartate receptor encephalitis; NREM: non-rapid eye movement; OMAS: opsoclonus-myoclonus-ataxia syndrome; OSA: obstructive sleep apnea; PDE10A: phosphodiesterase 10A; PERM: progressive encephalomyelitis with rigidity and myoclonus; PLMS: periodic limb movements in sleep; PSG: polysomnogram; PSP: progressive supranuclear palsy; RBD: rapid eye movement sleep behavioral disorder; SEZ6L2: seizure-related-6-homolog like autoimmunity; SCLC: small cell lung cancer; SPS: Stiff-person syndrome)

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binding (GluN1) subunit of the receptor to be demonstrated along with one or more of the six major groups of symptoms as mentioned earlier in the text.[3] Probable NMDARE is diagnosed when there are at least four out of six major groups of symptoms, with at least one of the supportive laboratory testing [abnormal electroencephalogram (EEG), CSF pleocytosis, or oligoclonal bands] **(Table 2)**.

Hyperkinetic crisis, dysautonomia, and differentiating true seizures from dyskinesias are potential challenges in management. Although uncommon, initial presentation with gyratory seizures could be an early clue pointing toward this disorder.[13] The anti-NMDAR Encephalitis One-Year Functional Status (NEOS) score is a useful tool for predicting the probability of poor functional outcome at 1 year, where one point each is given for ICU admission, delay in treatment for 4 weeks, absence of improvement within 4 weeks of treatment, abnormal magnetic resonance imaging (MRI), and CSF white blood cell count of >20 cells/μL.[14] Prompt administration of immunotherapy and removal of tumors when present are often rewarding. The treatment decisions should be primarily guided by clinical assessment as CSF antibody titers on follow-up do not correlate with the clinical course. A similar picture of prodromal fever and headache followed by neuropsychiatric disturbances, orofacial dyskinesias, seizures, dysautonomia, and altered sensorium can be present in neurexin 3α antibody-associated disorder.[11,15]

Anti-immunoglobulin-like Cell Adhesion Molecule Family Member-5 Disease

The earliest description of the anti-immunoglobulin-like cell adhesion molecule family member-5 (IgLON5) disease in 2014 came from a Sleep laboratory in Spain, following observation of patients having unique nonrapid eye movement (NREM) and rapid eye movement (REM) parasomnia with sleep breathing dysfunction, gait instability, and brainstem symptoms.[16] Features suggestive of both autoimmune mechanisms [such as anti-IgLON5 autoantibodies and a strong association with specific human leukocyte antigen (HLA)], as well as neurodegenerative diseases (hyperphosphorylated tau accumulations and limited response to immunotherapy), were subsequently reported.[17] The exact pathogenesis of this disorder remains unclear, with ongoing debate as to whether the immune abnormality is the cause or a consequence of a primary neurodegenerative process.[18] This disease, which has no specific gender predisposition, is a great mimicker and can present in older adults with clinical syndromes resembling a chronic degenerative disorder. Presentations with clinical features similar to progressive supranuclear palsy, multiple system atrophy, corticobasal syndrome, and motor neuron disease or with progressive dementia have been described; prominent sleep dysfunction out of proportion to that expected in the typical neurodegenerative syndromes could act as a diagnostic clue **(Table 2)**.[19] The sleep symptoms include NREM parasomnias, specifically "finalistic" movements, and REM parasomnias like REM sleep behavioral disorder (RBD). The IgLON5 composite score (ICS) is a severity assessment tool, which includes 17 symptoms distributed in five domains covering most of the clinical manifestations.[20] As antibodies are predominantly of the IgG4 subclass that is unable to activate complement-mediated immune reaction, poor response with intravenously immunoglobulin (IVIG) monotherapy is expected. Although combination therapy with rituximab, plasmapheresis, and IVIG works better if administered in the early phases, the overall prognosis of anti-IgLON5 disease is poor. A high-serum level of neurofilament light chain at diagnosis would predict a worse prognosis with immunotherapy.[17]

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Anti-Ma2/Ma1 Encephalitis

Anti-Ma2/Ma1 encephalitis is a diagnosis that needs to be considered in patients with isolated or combined limbic, diencephalic, or brainstem dysfunction. Ma2 and Ma1 antibodies tend to coexist in the same patient with the above-mentioned combination of clinical features, though Ma2 occurs at a higher frequency.[21] The presence of prominent diencephalic involvement (excessive daytime sleepiness, narcolepsy, or cataplexy) and upper brainstem involvement (e.g., atypical parkinsonism) with MRI abnormalities in the region distinguishes it from other paraneoplastic encephalitis syndromes.[21,22] Primary testicular neoplasm is a common association seen in young males, and lung cancer in the elderly.[21] The presence of additional Ma1 antibodies confers a worse prognosis as they have more extensive brainstem and cerebellar involvement and are associated with nontesticular cancers which, in turn, are more difficult to treat than testicular germ cell tumors. Features favoring improvement or stabilization with immunotherapy in a case of Ma2/Ma1 encephalitis include male gender, age <45 years, testicular tumor with complete response to oncological treatment, absence of anti-Ma1 antibodies, and limited CNS involvement.[21]

Anti-Homer-3 Antibody-mediated Disease

Anti-Homer-3 antibody-mediated disease is increasingly recognized as an autoimmune mimic of the cerebellar type of multiple system atrophy (MSA-C), characterized by cerebellar ataxia. Dysautonomia and REM-sleep behavioral disorders (RBD), with additional features like myeloradiculopathy, and encephalopathy may be seen.[23,24] There is no sex predilection, and the common age group affected is 40–50 years. CSF is mostly abnormal with inflammatory changes, but antibody detection can be challenging as currently available detection techniques have low sensitivity.[24] MRI also could be misleading with cerebellar/pontine atrophy and a "hot-cross bun" sign. They are not associated with malignancies and have variable responses to immunotherapy.[23]

Anti-Kelch-like Protein 11 Syndrome

A recent addition to the multitude of autoantibodies causing AMDs is the anti-Kelch-like protein 11 (KLH 11) syndrome.[25] They present as rapidly progressive ataxia, rhombencephalitis, and cochlea-vestibulopathy, discovered in patients with testicular seminoma.[26] They have poor response to immunotherapy owing to the intracellular nature of the target antigen. A clinical scoring validated termed MATCH (male sex:1 point, ataxia/cerebellar signs: 1 point, testicular tumor: 2 points, or other types of tumors: 1 point, hearing impairment: 1 point) helps in identifying conventional antibody-negative patients suspected to be harboring anti-KLH-11.[27]

Other AMDs include poststreptococcal and other postinfectious movement disorders [Sydenham chorea (SC), pediatric autoimmune neuropsychiatric disorder associated with streptococcal infection (PANDAS)], pediatric acute-onset neuropsychiatric symptoms (PANS) and systemic autoimmune conditions associated movement disorders [Sjögren syndrome, celiac disease, systemic lupus erythematosus (SLE) and antiphospholipid antibody (APLA) syndrome].[5,28] SC which is considered a part of rheumatic fever is the prototype example of acute to subacute childhood choreatic disorder, caused due to autoimmunity triggered by group A streptococcal infection.[29] It may be accompanied by neuropsychiatric morbidities and frequent relapses and remissions. No specific causative antibodies

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responsible for CNS inflammation have been demonstrated so far. Autoimmune basal ganglia encephalitis is at the rarer spectrum of pediatric AMDs, triggered by mycoplasma, Epstein–Barr virus, influenza, and Group A streptococcal infections.[29] It is characterized by parkinsonism, hyperkinetic movement disorders, sleep and neuropsychiatric disturbances, and autonomic dysfunction along with the presence of oligoclonal bands in CSF, without any evidence for an infective agent and responds to immunomodulation with steroids.[8]

Immune checkpoint inhibitors (ICI) are used for the treatment of cancer and act by neutralizing tumor evading T-cell immune responses. Though more often associated with autoimmune myasthenia, polyradiculoneuropathy, myositis, myelitis, and meningitis, widespread use of ICI is also postulated to be a risk factor for the increasing incidence of AMDs like limbic encephalitis and Ma2 encephalitis.[27,30]

WHEN TO SUSPECT AUTOIMMUNE MOVEMENT DISORDER?

The Graus criteria for AIE may be extrapolated to identify clues to suspect AMDs.[3] Subacute onset (<3 months), rapid progression, and presence of mixed movement disorders, accompanied by seizures, cognitive decline, altered sensorium, evidence for inflammation in CSF or MRI and propensity for autoimmunity or history of neoplasm should raise the suspicion of autoimmunity as a cause of the movement disorder.[3,29] Association with features suggestive of limbic encephalitis, subacute cerebellar degeneration, encephalomyelitis, and sensory neuronopathy also point toward autoimmunity, particularly of paraneoplastic etiology.[9]

Phenomenology in AMDs is difficult to classify due to the mixed presentations and coexisting abnormalities due to multifocal or diffuse involvement of neuraxis and peripheral nervous system (higher-level gait disorders, cerebellar ataxia, peripheral movement disorders like the ones resulting from peripheral nerve hyperexcitability and Stiff-person syndrome, and tremor and pseudoathetosis secondary to peripheral nerve involvement, etc.). It is also tricky sometimes to diagnose movement disorders in the background of active psychosis, irritability, and seizures (e.g., differentiating dystonia from focal tonic seizures in NMDARE). However, certain movement disorder phenomenologies should prompt the clinician to evaluate further for autoimmune etiology.[30]

Dystonia

Faciobrachial dystonic seizure in leucine-rich glioma-inactivated-1 (LGI1) related encephalitis is considered an immune-mediated paroxysmal movement disorder, occurring as brief (less than a few seconds) and frequent (100s/day) episodes of abnormal posturing of ipsilateral face and arm, poorly responsive to antiseizure medication and with a typically normal EEG.[1,30] Jaw dystonia and laryngospasm are typically seen in anti-Ri mediated encephalitis.[31] Dystonia of autoimmune etiology differs from isolated and combined genetic dystonic disorders in its anatomical distribution, age of onset, and temporal profile (generally occur acutely or subacutely) and usually is "combined", forming part of an encephalopathic syndrome, rather than occurring as an isolated manifestation.[7,30] AIE should be a differential diagnosis in the evaluation of dystonia with encephalopathy, particularly in children. The clinical phenomenology may mimic dopa-responsive dystonia (DRD) syndromes when NMDARE presents with oculogyric crises which is common in some DRDs.[7] Mitochondrial disorders in children may also present with dystonia and encephalopathy.

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Myoclonus

Myoclonus, particularly when it presents in a subacute manner with coexisting encephalopathy, should raise suspicion of acquired entities such as autoimmune encephalopathies, infections (prion disease and Whipple disease), and metabolic derangements (uremia and liver failure), most of which are treatable. Predominant orthostatic leg myoclonus is a characteristic phenotype associated with contactin-associated protein-like 2 (CASPR2) antibody-mediated autoimmune disorders.[7] Myoclonus is also a defining feature of opsoclonus-myoclonus-ataxia syndrome (OMAS), frequently associated with neuroblastoma in children. Paraneoplastic OMAS in adults is associated with breast and lung cancer.[7]

Chorea

Immune-mediated conditions need to be considered when chorea occurs acutely or subacutely both in children and in adults. SC, discussed above, is the classical immune-mediated choreatic disorder in children. Other immune choreatic disorders to be considered in adults include the APLA syndrome and rarer conditions such as anti-Hu, anti-collapsin response-mediator protein-5 (CRMP5), anti-phosphodiesterase 10A (PDE10A) and anti-neurexin-3α-related autoimmune encephalopathies. These are usually combined with additional neurological signs and symptoms and are often paraneoplastic in etiology **(Tables 2 and 3)**.[30]

TABLE 3: Differential diagnosis of autoimmune movement disorders (AMDs) based on each movement disorder phenomenology.

Movement disorder phenomenology	Target antigens of the associated autoantibodies
Chorea/unclassified dyskinesias[2,31]	CV2/CRMP5, Hu, CASPR2, LGI1, NMDAR, Neurexin-3α, GABAAR, Dopamine-2-R, IgLON5, and PDE10A
Dystonia [2,31]	NMDAR, LGI1, Ri, Dopamine-2-R, IgLON5, CV2/CRMP5, Ma2, and GABAAR
Myoclonus	CASPR2, LGI1, DPPX, Neurexin-3α, and GlyR
Opsoclonus–myoclonus syndrome	VGCC, NMDAR, DPPX, GABAAR, GABABR, GlyR, GAD, CV2/CRMP5, Hu, Ri, Ma2, Zic4, and Yo
Tremor	CASPR2, LGI1, NMDAR, DPPX, GFAP, and Yo
Myorhythmia	IgLON5 and NMDAR
Stiff-person syndrome	GAD, GlyR, Amphiphysin, Gephyrin, DPPX, GABAAR, and Ri
PERM	GlyR, GAD, and DPPX
Parkinsonism	Ma2, IgLON5, Dopamine-2-R, DPPX, LGI1, Ri, CV2/CRMP5, and NMDARE
Ataxia	CASPR2, DPPX, NMDAR, IgLON5, VGCC, mGluR1, GAD, Yo, Hu, Ri, PCA2, Zic4, SOX1, and GFAP
Sleep-related movement disorders	IgLON5, Ma, LGI1, NMDAR, DPPX, CASPR2, and GABABR

(AQP4: aquaporin-4; CASPR2: contactin-associated protein-like 2; CV2/CRMP5: collapsin response-mediator protein 5; DPPX: dipeptidylpeptidase-like protein-6; GABAAR: γ-aminobutyric acid A receptor; GABABR: γ-aminobutyric acid B receptor; GAD: glutamic acid decarboxylase; GFAP: glial fibrillary acidic protein; GlyR: glycine receptor; IgLON5: immunoglobulin-like cell adhesion molecule 5; LGI1: leucine-rich glioma-inactivated 1; mGLuR1: metabotropic glutamate receptor type 1; mGLuR5: metabotropic glutamate receptor type 5; NMDARE: N-methyl-D-aspartate receptor encephalitis; PCA2: Pürkinje cell antibody 2; PDE10A: phosphodiesterase 10A; VGCC: voltage-gated calcium channel; Zic4: zinc finger domain of the intracellular transcription factor)

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Peripheral Nerve Hyperexcitability and Related Conditions

Neuromyotonia (Issac syndrome) is a peripheral nerve hyperexcitability disorder clinically characterized by continuous muscle activity and manifesting as muscle stiffness, cramps, and myokymia. Morvan syndrome is a more severe condition with peripheral nerve hyperexcitability associated with myoclonus, encephalopathy, insomnia, neuromyotonia, and dysautonomia, seen in LGI-1 or CASPR2-related disorders.[31]

Stiff-person syndrome (SPS) is a clinical diagnosis characterized by fluctuating trunk and proximal limb (predominantly legs) rigidity, superimposed spasms, and exaggerated startle response (hyperekplexia), supported by the presence of autoantibodies.[7,32] Painful spasms are provoked by loud noise, touch, emotion, and stress, and are relieved dramatically with diazepam.[28,31] The presence of SPS, especially among females aged 40–60 years, should trigger a search for antibodies against glutamic acid decarboxylase (GAD), amphiphysin, gephyrin, glycine receptor (GlyR), dipeptidyl peptidase-like protein-6 (DPPX), and γ-aminobutyric acid A receptor (GABAAR).[7] Paraneoplastic SPS associated with anti-amphiphysin antibodies affects the older population, has a predilection for the upper limbs and neck region, and may be associated with myelopathy and sensory neuropathy.[7,28] Progressive encephalomyelitis with rigidity and myoclonus (PERM) is more often seen with GlyR antibodies and has an aggressive course with brainstem and autonomic dysfunction and long-tract signs.[8,28]

Other Movement Disorders

Tics form part of the clinical spectrum of PANDAS.[7] There have been unresolved debates on the epidemiology and pathophysiology of this entity and there are no evidence-based treatment recommendations. There are also certain sleep-related movement disorders described in autoimmune disorders affecting the CNS. Examples include status dissociatus (disintegration of stages of sleep boundaries with motor hyperactivity) and agrypnia excitata (insomnia, motor, and autonomic hyperactivity), which are seen in Morvan syndrome with anti-CASPR2,[30] and some other autoimmune encephalopathies.

The AMDs to be suspected based on a particular phenomenology are outlined in **Table 3**.

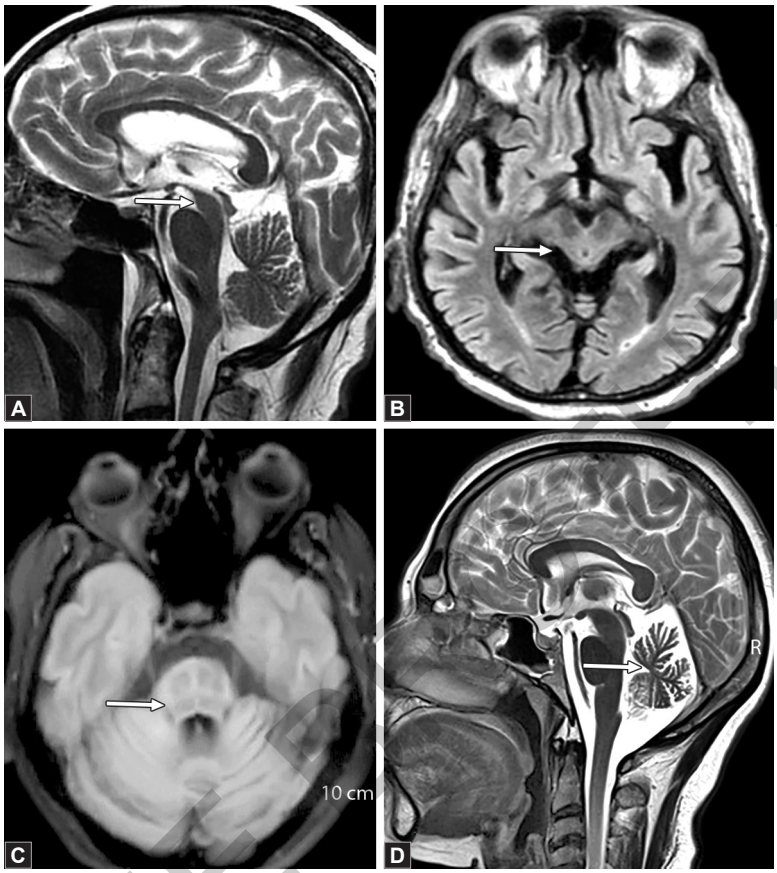
Knowledge regarding the distinct phenotypes and high index of suspicion is essential for diagnosing AMD and early initiation of immunotherapy.

Investigations in Suspected Autoimmune Movement Disorders

The investigations suggested for the workup of AMDs include MRI of the brain, CSF study, EEG, investigations like imaging studies, histopathology and tumor markers for underlying malignancy, and specific autoantibody testing. The positive findings favoring a diagnosis of AMD are mainly related to signs of inflammation in CSF (pleocytosis, elevated protein, IgG index, and oligoclonal bands) and MRI brain (T2 hyperintensities and gadolinium enhancement). **Figures 1 and 2** demonstrate representative MR images in selected AMDs.

There are various laboratory methods available for testing for autoantibodies. Western blot, indirect immunofluorescence (IFA), and immunohistochemistry (IHC) are essentially screening tests. To increase the specificity in the case of atypical clinical phenotypes, cell-based assays (CBA) are also recommended.[7] The interpretation of antibody testing results differs depending on the sample used. Antibodies to aquaporin P4 (AQP4) or voltage-gated potassium channels

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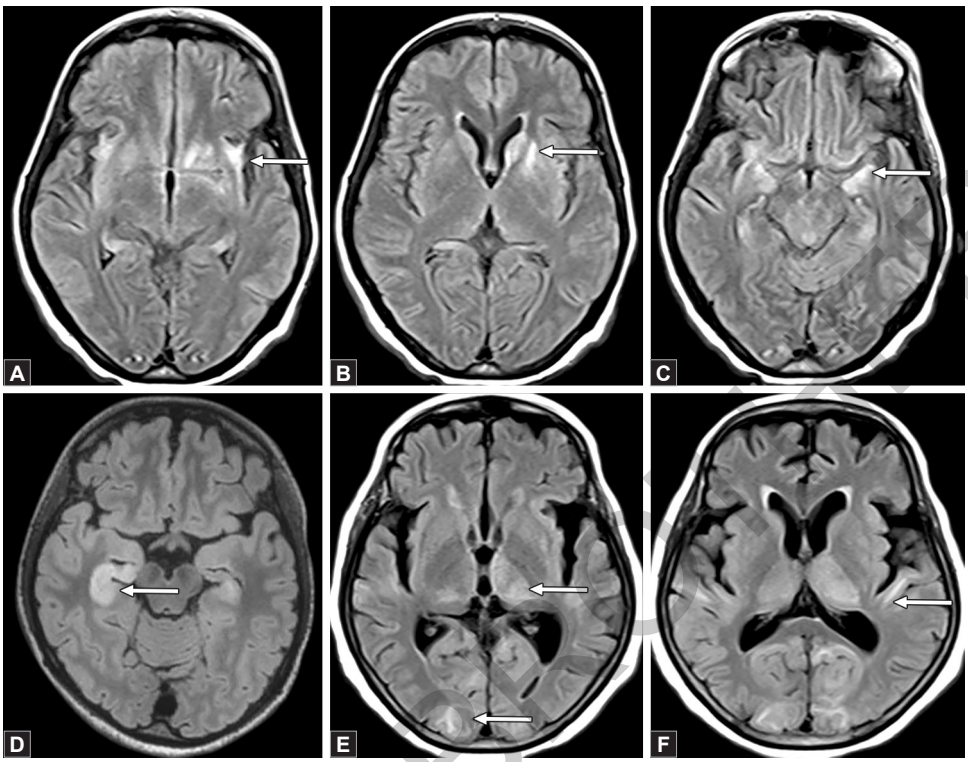
FIGS. 1A TO D: Magnetic resonance imaging (MRI) of the brain in autoimmune movement disorders. (A and B) Show T2-weighted sagittal and axial fluid-attenuated inversion recovery (FLAIR) sequences from a 54-year-old gentleman who presented with subacute onset axial parkinsonism from anti-immunoglobulin-like cell adhesion molecule family member 5 (IgLON5) antibody-related disease. The images show midbrain atrophy. (C) is the axial FLAIR image from a 62-year-old lady who presented with progressive ataxia, sleep dysfunction, and subtle parkinsonism. Cerebrospinal fluid (CSF) anti-IgLON5 antibodies were positive. The image shows "hot-cross-bun sign". (D) Shows T2-weighted sagittal image of the brain of a 50-year-old lady with anti-Yo encephalitis. The image shows significant cerebellar vermian atrophy.

(VGKC) are readily detected in serum, whereas others like anti-NMDAR or anti-GlyR are more relevant when demonstrated in CSF.[33] This could be largely due to technical factors leading to easier detection of these antibodies in CSF compared to serum or due to intrathecal antibody synthesis.[7] Overall, sensitivity and specificity are highest when both serum and CSF are tested **(Table 3)**.

SERONEGATIVE AUTOIMMUNE MOVEMENT DISORDER

Newer antibodies are being constantly added to the group of autoantibodies associated with neurological disorders every year, and hence it is obvious that there could be "antibody-negative" cases of autoimmune neurological disorders whose immunopathology is yet to

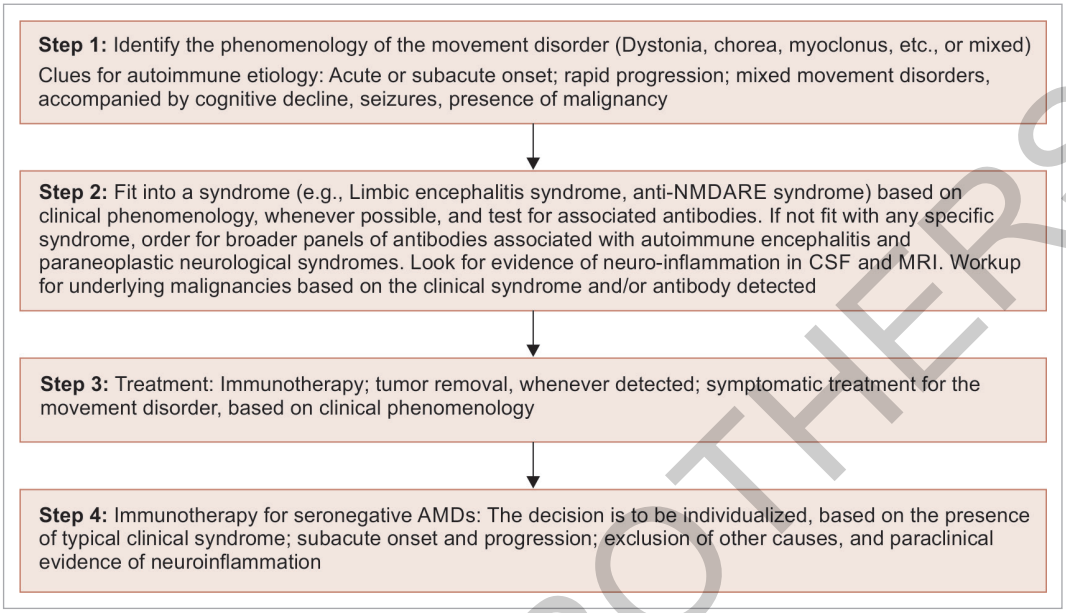
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FIGS. 2A TO F: The images in the upper panel (A to C) show axial fluid-attenuated inversion recovery (FLAIR) sequences from a 50-year-old lady who presented with subacute onset encephalopathy and generalized dystonia. The images show hyperintensities in the basal ganglia, insula, and medial temporal lobes. Antibody testing was negative and the patient responded to immunotherapy. (D) Shows bilateral hippocampal hyperintensity in axial FLAIR sequences, in a 35-year-old lady with limbic encephalitis who was also antibody-negative. (E and F) Show multiple thalamic, cortical, and subcortical hyperintensities in a 72-year-old lady with anti-Ri encephalitis (arrows).

be discovered. Increased awareness regarding autoimmune neurological disorders has led to an increase in the diagnosis and sometimes overdiagnosis of AMDs in seronegative patients. The most important reasons for misdiagnosis include nonadherence to diagnostic criteria (particularly, exclusion of alternate diagnosis), failure to look for and give weightage to inflammatory changes in CSF and MRI, and limited use or unavailability of antibody testing.[34] Considering the treatability factor, the clinician is often biased toward making a diagnosis of seronegative AMD without adequate workup. When deciding the management strategy in seronegative AMDs, the treating physician needs to judiciously weigh the potential toxicity of the available immunotherapy options against the treatability factor, likelihood of an autoimmune etiology for the neurological syndrome in question, and chances of a progressive downhill course if immunotherapy is not administered **(Flowchart 1)**. Guidelines have been proposed to diagnose autoimmune encephalopathies when testing shows no autoantibodies.[34] These could be adapted to make a diagnosis of seronegative AMDs.

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FLOWCHART 1: Algorithm for evaluation and management of suspected autoimmune movement disorder (AMD).

(CSF: cerebrospinal fluid; NMDARE: N-methyl-D-aspartate receptor encephalitis)

The following features should lead to a high index of suspicion for AMDs even when antibody testing is negative:

- Rapid progression (<3 months) of the movement disorder with or without working memory deficits, altered mental status, and psychiatric symptoms.
- At least two of the following features suggesting inflammation of the brain: (1) MRI abnormalities suggesting AIE, (2) CSF pleocytosis, CSF-specific oligoclonal bands, or elevated CSF IgG index in the absence of any infection, and (3) brain biopsy showing inflammatory infiltrates.
- Reasonable exclusion of alternative causes

Alternative diagnoses to be excluded in patients with symptoms suggestive of AMDs include, but are not limited to the following: CNS infections (Herpes simplex encephalitis, Japanese encephalitis, neurosyphilis), Whipple disease, human immunodeficiency virus (HIV), Creutzfeldt–Jakob disease, septic encephalopathy, metabolic encephalopathy (uremia, liver failure, carbon monoxide poisoning, etc.), drug toxicity, Reye syndrome, "brain fog" (deficits in memory, attention, and executive functions) occurring as a result of chemotherapy, polypharmacy, or postcoronavirus disease (COVID), first onset psychosis and psychiatric disorders, functional movement disorders, epileptic disorders, mitochondrial diseases and neurometabolic disorders, neoplastic disorders (mainly glioma and lymphoma), vasculitis of CNS and rapidly progressive neurodegenerative or genetic disorders.

PRINCIPLES OF MANAGEMENT

Symptomatic treatment of movement disorders in autoimmune neurological syndromes is summarized in **Table 4**. The symptomatic treatment of movement disorders should be accompanied by correcting the metabolic derangements, such

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Advances in Movement Disorders

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Printed in India

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Medical Publishers (P) Ltd.
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ISBN 978-93-5316-796-7