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Review Article

Autoimmune and paraneoplastic movement disorders: An update

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ABSTRACT

Movement disorders (MDs) are common in patients with autoimmune disorders affecting the central and peripheral nervous system. They may be observed in autoimmune disorders triggered by an infectious agent, such as streptococcus in Sydenham's chorea, or in basal ganglia encephalitis with antibodies against the dopamine-D2 receptors. In these patients chorea or dystonia are usually the most prominent hyperkinetic MDs. MDs are also observed in patients with diffuse or limbic encephalitis with antibodies directed against neuronal cell-surface antigens. Anti-NMDA receptor encephalitis is one of the most common and may present with a variety of MDs, including: chorea, stereotypies, dystonia and myorhythmia. The recognition of other abnormal motor phenomena such as "faciobrachial dystonic seizures" and neuromyotonia, observed in patients with LGI1 and Caspr-2 antibodies, is important because they may herald the onset of overt limbic encephalitis. Autoimmunity directed against the intracellular enzyme glutamic acid decarboxylase usually presents with MDs, most commonly stiff-person syndrome or cerebellar ataxia. Chorea may be observed in rheumatologic disorders such as systemic lupus erythematosus or antiphospholipid syndrome. Disorders with uncertain autoimmune mechanisms such as Hashimoto's encephalitis and idiopathic opsoclonus-myoclonus syndrome commonly present with tremor, myoclonus and ataxia. A rapid diagnosis of an autoimmune disorder, which typically presents with subacute onset, is critical as early therapeutic intervention improves long-term prognosis and may be life-saving. Treatment usually involves some form of immunotherapy and symptomatic therapy of the abnormal movements with dopamine depleters, dopamine receptor antagonists, or GABAergic drugs. Detection and removal of an underlying tumor is essential for optimal outcome.

1. Introduction

The discovery of a variety of antibodies over the past few decades has helped to characterize the clinical syndromes of several autoimmune disorders of the nervous system. Movement disorders (MDs) are observed in many of these entities and its subacute onset is often a clue for the diagnosis. In this review, we discuss recent advances in these disorders. We excluded MDs within the spectrum of demyelinating disorders such as multiple sclerosis, and neurodegenerative disorders such as Parkinson's disease in which autoimmunity has been proposed to play a role [1,2].

2. Parainfectous movement disorders (Table 1)

2.1. Sydenham's chorea

Sydenham's chorea (SC) is a childhood-onset, delayed manifestation of GABHS infection and a major component of rheumatic fever (RF). Chorea presents in about 26% of patients with RF [3], it is usually asymmetrical, although pure hemichorea is observed in about 20% of

Abbreviations: AMPA, α-amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid; ANNA, anti-neuronal nuclear antibody; APS, antiphospholipid syndrome; ARHGAP26, Ca/RhoGTPase-activating protein 26; CaMKII, calcium calmodulin-dependent protein kinase II; CASPR2, contactin-associated protein-like 2; CARP VIII, carbonic anhydrase related protein VIII; CDRP, Cerebellar degeneration-related protein; CF, cyclophosphamide; CRMP-5, collapsin-response mediator protein 5; DM1, diabetes mellitus type 1; DNER, Tr/delta notch-like epidermal growth factor (EGF)-related Receptor; DPPX6, dipeptidyl peptidase-like protein 6; GABA, γ-Aminobutyric acid; GABHS, group A β-hemolytic streptococcus; GAD, glutamic acid decarboxylase; GlcNAc, N-acetyl-beta-D-glucosamine; GluRδ2, glutamate receptor delta 2; Homer-3, Homer protein homolog 3; IVIg, intravenous immunoglobulin; LGI1, leucine rich glioma inactivated protein 1; MDs, movement disorders; mGluR1, metabotropic glutamate receptor 1; NMDA, N-Methyl-D-Aspartate; OMS, opsoclonus-myoclonus syndrome; PANDAS, pediatric autoimmune neuropsychiatric disorder associated with streptococcus; PANS, pediatric acute-onset neuropsychiatric syndrome; PCA, Purkinje cell cytoplasmic antibody; PKCγ, protein kinase C gamma; RF, rheumatic fever; Sj/ITPR1, Sj/inositol 1,4,5-triphosphate receptor; SLE, systemic lupus erythematosus; SREAT, steroid responsive encephalopathy associated with autoimmune thyroiditis; TMS, transcranial magnetic stimulation; VGCC, voltage-gated calcium channels; VGKC, voltage-gated potassium channel

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Table 1
Clinical features, antibody profile and treatment of autoimmune conditions associated with movement disorders.

Disorder	Typical age at onset/ gender predilection	Antibodies	Tumor frequency	Main neuropsychiatric manifestations	Movement disorders
Sydenham's disease	5 to 15 years/female preponderance	Lysoganglioside Tubulin D1 and D2 dopamine receptor	0%	Obsessive compulsive behavior, abnormal verbal fluency and prosody, seizures, dysexecutive syndrome	Chorea (F) Tics Hypotonia Oculogyric crises
PANDAS or PANS	3 years to puberty/ male preponderance	Same as Sydenham's disease	0%	Obsessive compulsive behavior, separation anxiety, enuresis, night fears, anorexia, etc.	Tics (F) Chorea minima (F)
Basal ganglia encephalitis	< 1 to 15 years/equal gender distribution	Dopamine-2 receptor	0%	Emotional lability, attention deficit, psychosis	Dystonia (F) Parkinsonism, (F) Chorea (F)
Anti-NMDA receptor encephalitis	23 years/4 times more common in females, except in extremes of life.	NMDA receptor (NR1 subunit)	58% in women > 18 years (Ovarian > testicular teratoma)	Delusions, agitation, hallucinations, speech dysfunction, memory deficits dysautonomia, seizures, central hypoventilation, decreased level of consciousness, hemiparesis	Chorea, stereotypies, catatonia, dystonia, myorhythmia (F) Cerebellar ataxia (U)
Post-herpes simplex encephalitis	24–79 years/equal gender distribution	NMDA receptor (NR1 subunit) D2 dopamine receptor $GABA_A$ receptor	0%	Psychiatric manifestations	Choreoathetosis (F)
Encephalitis (diffuse or limbic)	64 years/male twice more commonly affected	LGI1	5–10% (Thymoma)	Behavioral changes Seizures (several types) Amnesic syndrome Hyponatremia REM-sleep behavior disorder	Faciobrachial dystonic seizures (F)
	40 years/male preponderance	$GABA_B$ receptor	50% (SCLC)	Encephalopathy, seizures	Ataxia, opsoclonus, chorea, lingual dyskinesia (U)
	56 years/women 70% of cases	AMPA receptor	65% (SCLC, thymoma)	Encephalopathy, seizures	Ataxia (U) SPS phenomena (U)
	40 years/male gender (more common)	$GABA_A$ receptor	< 5% (Thymoma)	Encephalopathy, seizures	SPS phenomena (U) Opsoclonus-myoclonus (U) Catatonia (U)
Morvan's syndrome	57 years/almost exclusively in males	CASPR2 LGI1 (less common) Contactin-2 (less common)	20–50% (Thymoma)	Psychosis, insomnia, agrypnia excitata, dysautonomia (hyperhidrosis, cardiovascular instability), peripheral neuropathy	Neuromyotonia, cramps, fasciculations (F)
Progressive encephalomyelitis with rigidity and myoclonus (PERM)	50 years/male preponderance	Glycine1 receptor DPPX-6	< 20%	Encephalopathy, brainstem dysfunction, dysautonomia, sensory symptoms	Stiffness/rigidity (F) Stimulus-sensitive spasms (F) Myoclonus (F) Hyperekplexia (F) Ataxia (F)
Parasomnia associated with IgLON-5 antibodies	64 years/equal gender distribution	IgLON-5	0%	Abnormal non-REM & REM sleep, stridor, obstructive sleep apnea, dysphagia, vocal cord paresis, dysarthria, hypoventilation, altered ocular movements, dysautonomia	Severe gait instability (F) Rapid periodic leg movements (F) Chorea (F) Mandibular spasms (U)
Hashimoto's encephalopathy (SREAT)	45–55 years/5 times more common in females	Thyroid peroxidase Thyroglobuline α-Enolase	0%	Confusion, seizures, stroke-like episodes, REM-sleep behavior disorder	Myoclonus (F) Tremor (F) Ataxia (F)
Opsoclonus-myoclonus syndrome	45 years/slight female preponderance	Ri/ANNA2 Glycine1 receptor NMDA receptor $GABA_B$ receptor $GABA_A$ receptor Human natural killer (HNK-1)	40% (Lung and breast cancer)	Opsoclonus	Myoclonus (F) Tremor (F) Gait ataxia (F)

Frequent (F): present in ≥ 25% of patients in most series; uncommon (U): present in < 25 of cases in most series.

cases; associated severe hypotonia presents in about 8% of cases leading to bedridden, a condition known as: “chorea paralytica”. Other motor phenomena include motor impersistance (“milkmaid's grip” and “darting tongue”), phonic or motor tics; altered ocular fixation and oculogyric crises [4]. Chorea usually antedates other neuropsychiatric manifestations like obsessive compulsive symptoms, impaired verbal fluency or a dysexecutive syndrome [5]. A major concern in patients with SC is cardiac involvement, which presents in between 60% and 80% of cases [3]. Because of many neurologic, psychiatric, rheumatologic, cardiac and other co-morbidities the condition should be called “Sydenham's disease” rather than SC, but the latter has been traditionally used in the medical literature.