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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.

The diagnosis of SC is supported by demonstration of a previous infection with GABHS using throat cultures, or positive anti-streptolysin O or anti-DNAse antibodies. MRI is usually normal, although an increase in basal ganglia (BG) volume has been reported using volumetric methods. Anti-BG antibodies have been observed with a high sensitivity (95%) in patients with acute SC [5,6]. However, these antibodies are not available for commercial testing and it is unclear how to define positivity. Furthermore, these antibodies do not seem very specific for SC and have been shown to react with D1 and D2 dopamine receptors as well as with neuronal tubulin, and lysoganglioside [7,8]. The antibodies against the latter antigen show cross-reactivity with the carbohydrate epitope GlcNac of GABHS [8]. It seems that these antibodies activate the CaMKII pathway of neurons leading to an increase in dopamine release, possibly explaining the chorea and some of the neuropsychiatric manifestations of SC [8]. Unfortunately, these antibodies have not shown a clear pathogenic role and have low specificity because they may also be present in patients with Parkinson's disease and Huntington's disease; moreover, the antibodies bind to cerebral structures outside the BG; therefore, the term anti-neuronal, rather than anti-BG may be more appropriate [5].

2.2. PANDAS and PANS

The terms, “PANDAS” has been proposed to explain a disorder triggered by GABHS infections and manifested by young-onset obsessive compulsive behavior, followed by tics and choreiform movements of fingers and toes that may be associated with poor handwriting skills [4,9]. These patients share a set of antibodies similar to those with SC. Although the concept of “PANDAS” is controversial and its existence has been questioned due to lack of consistent link with GABHS infections, other microorganisms such as *Mycoplasma* or influenza, and Lyme disease have been proposed to be associated with a similar disorder, which has led to coin the term “PANS” [9]. Despite this change in terminology, the existence of PANDAS/PANS as a nosologically distinct disorder is doubtful.

2.3. Basal ganglia encephalitis

Basal ganglia (BG) encephalitis typically presents with psychiatric manifestations and MDs [10]. The subacute onset is usually during childhood with equal gender distribution. Lesions in the BG have been found in about half of cases assessed by MRI [10]. Dystonia with dystonic tremor is the most frequent MD, observed in 10 out of 17 patients in one series [10], followed by parkinsonism, chorea and oculogyric crises. Most cases occur after an infection (particularly β-hemolytic streptococcus, mycoplasma or enterovirus) or vaccination. The pathogenic role of anti-D2 dopamine antibodies is yet to be clarified; however, they were found positive in 10 out of 30 patients with SC, suggesting a possible and poorly defined overlap between BG encephalitis and SC [10]. A similar clinical presentation, with CSF oligoclonal bands, improvement with steroids as well as lack of influenza virus RNA in pathological specimens has led to theorize that encephalitis lethargica represented a form of autoimmune BG encephalitis [11].

2.4. Post-herpes simplex encephalitis

A relapsing form of herpes simplex encephalitis, occurring in about 20% of patients after the initial illness, has been shown to be associated with the presence of anti-NMDA receptor antibodies in the serum or CSF [12–14]. Antibody synthesis of several isotypes (IgG, IgA or IgM) usually starts 1 to 4 weeks following the initial viral infection and may precede the onset of neurological symptoms associated with the relapse. Choreoathetosis, with or without orofacial and lingual dyskinesia, is a common presentation in children [15]; these patients usually improve with immunotherapy similar to that employed for anti-NMDA receptor (NMDAR) encephalitis (see discussion below).

3. Movement disorders in autoimmune encephalitis with antibodies against plasma membrane proteins

3.1. Anti-N-methyl-D-aspartate receptor (NMDAR) encephalitis

Anti-NMDAR-encephalitis is considered the most common autoimmune encephalitis. It affects predominantly young individuals with a mean age at onset of 23 years; women are affected 4 times more frequently than men, but female predominance is less prominent in individuals younger than 12 years and older than 45 years [16]. A substantial proportion of young females with NMDAR-encephalitis have underlying ovarian teratomas, but also various carcinomas have been reported, especially in adults. The diagnosis is usually suspected by subacute presentation of behavioral and neurologic (encephalopathic) symptoms, and is supported by an abnormal EEG and CSF with pleocytosis and oligoclonal bands. Definite diagnosis is based on the detection of IgG against the NR1 subunit of the NMDA receptor, particularly in the CSF [17].

Anti-NMDAR-encephalitis is characterized by the onset of neuropsychiatric manifestations, followed by speech dysfunction, memory deficits, dysautonomia, decreased level of consciousness and a broad variety of MDs [16]. MD is the predominant presentation in children younger than 12 years, with decreased frequency in older age groups [9]. Several MDs have been described in these patients including: chorea, stereotypies, dystonia, catatonia, myoclonus, tremor, opsoclonus-myoclonus and cerebellar ataxia [18–20]. Orofacial dyskinesia is typical and may correspond to dystonia, stereotypy or myorhythmia, the latter is characterized by slow (1–4 Hz), repetitive, rhythmic movements, affecting cranial or limb muscles [21]. In a study comparing children with NMDAR-encephalitis with BG-encephalitis and SC, the former had a significantly higher frequency of stereotypies and motor perseveration [22]. The hyperkinetic disorders associated with NMDAR-encephalitis usually respond to dopamine depleting drugs, such as tetrabenazine, deutetrabenazine and valbenazine [23].

3.2. Limbic and other autoimmune encephalitis

Limbic encephalitis (LE) is characterized by subacute onset with rapid progression in < 3 months of working memory deficits, confusion, mood changes and seizures, along with bilateral hyperintensities on MRI, highly restricted to the medial temporal lobes [17]. LE patients usually have one of two types of antibodies: 1) onconeural, more commonly ANNA-1 (anti-Hu) and anti-Ma2, frequently associated with underlying cancer and 2) neuronal cell surface antibodies, including: anti-VGKC complex: LGI1 and Caspr-2; $GABA_B$ receptor and AMPA receptor antibodies. Although the presence of such antibodies is not absolutely necessary for the diagnosis of LE, a positive result supports it and helps to define prognosis and risk of comorbidities (Table 1) [17].

Antibodies directed against the VGKC-complex are among the most common antibodies encountered in patients with LE. These antibodies, however, are not directed against potassium channels but to the associated proteins: LGI1 and Caspr-2, and less commonly to contactin-2 [24]. A minority of individuals have VGKC positivity without antibodies for any of these 3 antigens. This group is heterogeneous without well-defined underlying neurological syndromes [24,25]. Antibodies against LGI1 and Caspr-2 are likely pathogenic as they are associated with well-defined clinical syndromes [24,26]. Anti-LGI1 encephalitis is one of the most common syndromes, with half of patients presenting with the so-called “faciobrachial dystonic seizures”, which are brief and frequent involuntary dystonic movements affecting mainly the arm and ipsilateral face usually preceding the onset of LE, although few cases never develop LE [27]. EEG does not always show abnormal activity and antiepileptic drugs are usually ineffective, whereas prominent response to immunotherapy has been observed. Pain, peripheral nervous system manifestations and paroxysmal dizziness spells are increasingly recognized as common in patients with LGI1 antibodies [26]. Patients

Fig. 1. A) hypertrophy of paraspinal muscles in a patient with SPS: B) classical lumbar hyperlordosis in the same patient.

with antibodies against Caspr-2 have a more variable presentation with central and peripheral nervous system manifestations [24]. Neuromyotonia (Isaac's syndrome) is part of such phenomenology and manifests with stiffness, spontaneous muscle contractions and impaired relaxation. EMG usually shows bursts of high frequency random muscle discharges [24]. When neuromyotonia combines with encephalopathy and dysautonomia the disorder is called Morvan's syndrome [28]. This disorder presents almost exclusively in males, with neuromyotonia usually preceding the onset of encephalopathy [28].

Other antibodies directed against membrane receptors such as AMPA, $GABA_B$ and $GABA_A$ may be observed in patients with encephalitis [29–35]. Although several MDs have been described in these patients; the presentation is usually dominated by encephalopathy and seizures (Table 1).

3.3. PERM

Progressive encephalomyelitis with rigidity and myoclonus (PERM) is a disorder characterized by relapsing-remitting course of altered level of consciousness, dysautonomia, and brainstem manifestations with prominent myoclonus, hyperekplexia, cerebellar ataxia, stimulus-sensitive spasms and axial and limb rigidity [36,37]. The latter may resemble features observed in stiff-person syndrome (SPS), therefore PERM has been considered within the spectrum of this disorder. However, more recent evidence links it with antibodies against the α1 subunit of the glycine receptor (GlyR) and with GAD antibodies [36,38,39]. Furthermore, patients with PERM usually show pathological signs of encephalomyelitis with perivascular lymphocytic cuffing, which contrasts with paucity of inflammatory changes in autopsy studies of SPS patients; although with little evidence of inflammation on neuroimaging. Most patients affected by PERM are in their fifth or sixth decades of life, while SPS can affect any age group, including children [40]. A syndrome similar to PERM, but frequently accompanied by diarrhea and other gastrointestinal symptoms [41,42], has been associated with antibodies against DPPX-6, which is a regulatory subunit of the Kv4.2 potassium channel, a protein highly expressed in the enteric plexus that can become hyperexcitable following exposure to these antibodies [43].

3.4. Anti-IgLON 5

A novel syndrome characterized by sleep disorders and by brainstem and hypothalamic manifestations has been found to be associated with antibodies against the neuronal cell adhesion protein IgLON5 [44]. Patients with IgLON5 antibodies have a median age at onset of 64 years with equal gender distribution [45] and typically present either with a complex sleep disorder, severe gait instability, or chorea predominantly affecting the limbs although orofacial dyskinesia may be also present [44]. Cognitive decline with or without chorea was the predominant presentation in 14% in a recent series of 22 patients [45]. Patients frequently have rapid periodic leg movements during wakefulness that may briefly continue following sleep onset. A characteristic aggregate of tau protein in the tegmentum and brainstem was observed in pathological samples of 2 individuals [44]. Oculomotor dysfunction is common with 23% of cases presenting a syndrome resembling progressive supranuclear palsy (PSP). The lack of response to immunotherapy with sudden death during sleep or wakefulness and underlying neurodegenerative disorder casts doubts about the autoimmune basis of these cases.

4. Movement disorders associated with anti-GAD antibodies

4.1. Stiff-person syndrome

Stiff-person syndrome (SPS) is the classical presentation of autoimmune disorders associated with antibodies against the enzyme GAD [46]. Most cases present between the fourth and sixth decade of life (although SPS has been also described in children), and women outnumber men 5 to 1.

The disorder is characterized by increased tone of axial and limb muscles, with superimposed muscle spasms leading to lumbar hyperlordosis (Fig. 1), impaired gait and falls [46,47]. Dysautonomic crisis with profuse diaphoresis, tachycardia and hypertension is another feature of SPS. Muscle rigidity and spams may result in several complications including: dyspnea, poor exercise tolerance, joint dislocation or bone fractures [46]. Some patients may manifest prominent stimulus-sensitive myoclonus affecting axial and proximal limb muscles, “jerking stiff-man syndrome”. Other clinical variants include: focal or partial SPS and paraneoplastic SPS, the latter is chiefly associated with anti-amphiphysin antibodies and breast cancer [46]. EMG of patients with SPS shows continuous motor unit activity in agonist and antagonist muscles. The origin of such activity is presumably secondary to GAD-induced disinhibition leading to impairment of neurons to produce, transport and release GABA into the synaptic cleft. However, this is a matter of debate as the enzyme GAD is intracellular and experimental models have failed to show a direct pathogenic effect of such antibodies [48]. Decrease in the GABAergic tone in the spinal cord's interneurons does not fully explain the continuous motor activity and altered exteroceptive reflexes observed in these patients [49,50]. However, there is evidence of supraspinal dishinbition based on the observation of decreased cortical GABA measured by MR-spectroscopy, altered flumazenil binding-potential on PET and impaired cortical inhibition assessed by TMS [51,52]. Nearly all patients with SPS have an associated autoimmune disease, such as DM1, thyroid, pernicious anemia, and vitiligo.

4.2. Cerebellar ataxia

Anti-GAD cerebellar ataxia (CA) is the second most common neurological syndrome associated with positive serum GAD antibodies after SPS [53]. Women represent > 80% of cases, with a median age at onset of 59 years. Most patients have a subacute (between 3 and 6 months) or chronic (> 6 months) course [53]. Patients usually present with a pancerebellar syndrome and prominent oculomotor dysfunction including nystagmus. In 20% of cases the CA is preceded by transitory

Table 2
Differential diagnosis of autoimmune cerebellar ataxias.

	Anti-GAD	Gluten sensitivity	Cerebellar type of HE	SLE Ataxia
Gender	85% female	50% (female)	50% (female)	> 90% (female)
Age at onset	58 years	48 years	53 years	20–40 years
Evolution	Subacute or chronic	Chronic	Acute to chronic	Acute or subacute
Clinical manifestations	Gait and limb ataxia, nystagmus is frequent. SPS phenomena and epilepsy may coexist	Gait and limb ataxia, nystagmus, sensorimotor axonal neuropathy, myoclonus, palatal tremor, opsoclonus, chorea	Gait ataxia (main), nystagmus infrequent (17%); neuropsychiatric symptoms	Pancerebellar syndrome, brainstem or cranial nerve dysfunction
Antibodies	GAD	Gliadin Transglutaminase-2 Transglutaminase-6	Thyroglobulin Thyroid peroxidase NH2-terminal α-enolase	Purkinje's Cell (75 kDa) Nuclear dsDNA Cardiolipin (IgG and IgM)
Investigations	MRI: mild cerebellar atrophy Intrathecal production of GAD abs	MRI: mild cerebellar atrophy, White matter hyoerintensities. MRS: reduction of NAA/Cr ratio in the vermis	MRI: mild cerebellar atrophy. EEG: slow waves.	MRI: cerebellar atrophy, ischemic lesions in the brainstem and cerebellum; small hyper intensities in the WM.
Associated autoimmune disease	DM1, thyroiditis, pernicious anemia.	DM1, thyroiditis, pernicious anemia.	Thyroiditis	APS
Therapy	Steroids, IVIg, Rituximab, azathioprine.	Gluten-free diet IVIg in refractory cases MM for myoclonic ataxia.	Steroids (highly effective)	Steroids, Azathioprine Cyclophosphamide (monthly pulses) Anticoagulation (in case of ischemia)

APS: antiphospholipid syndrome; dsDNA: double-stranded DNA; HE: Hashimoto's encephalopathy; MM: mycophenolate mofetil; MRI: magnetic resonance imaging; MRS: magnetic resonance spectroscopy; NAA/Cr: *N*-acetylaspartate/creatine.

episodes of brainstem dysfunction: “brainstem attacks” [54]. About 50% to 70% of patients have a coexistent autoimmune disorder such as DM1, thyroiditis, polyendocrine autoimmune disease, vitiligo, pernicious anemia and myasthenia gravis, similar to what is observed in patients with SPS [53,54]. Treatment is based on immunosuppression.

Anti-GAD CA was the second most common autoimmune ataxia after “gluten ataxia”, in a prospective study of 1500 patients with sporadic progressive ataxia [55]. Gluten ataxia is associated with anti-gliadin and anti-transglutaminase antibodies plus uncommon enteral pathology [55,56]. Robust improvement can be achieved with a diet restricted in gluten. It is unclear why practically all reports of gluten ataxia come from the same geographic area in the United Kingdom, despite the fact that gluten sensitivity is a widely distributed disorder. Differential diagnosis should also include other autoimmune cerebellar syndromes (Table 2) [57].

5. Movement disorders in rheumatic diseases

5.1. Systemic lupus erythematosus and antiphospholipid syndrome

Chorea is the most frequent MD observed in SLE and APS with prevalence between 1% and 3%, and it may be the initial presentation, even before patients fulfill all diagnostic criteria for SLE or APS [5,58]. Women represent > 90% of cases with a median age at onset between 15 and 26 years. The movements usually coexist with neuropsychiatric manifestations such as abnormal behavioral or frank psychosis [58]. PET scans using ^{18}F-deoxyglcose have shown increased metabolism in the contralateral striatum. The pathogenesis of chorea in these patients is not yet understood; antiphospholipid (aPL) antibodies may play a role through disruption of the blood brain barrier, allowing other antibodies to reach the CNS. Indeed aPL antibodies are positive in up-to 90% of patients with lupus chorea and arterial thrombotic events are not uncommon in these patients [59]. Moreover, chorea may be observed in patients with positive aPL antibodies or in those that meet criteria for APS, but not for SLE [60]. It is unclear what causes chorea in SLE patients with negative aPL antibodies. Anti-NMDAR antibodies against subunits NR2a and NR2b have been implicated in behavioral and cognitive changes in patients with SLE but not in chorea or other involuntary movements [58]. Treatment with a dopamine depleter, valproic acid or carbamazepine usually ameliorates chorea. Antiplatelet or anticoagulants should be added in case of positive aPL antibodies. In case of lack of improvement or present of systemic manifestations, pulses of steroids or cyclophosphamide should be considered [61].

Parkinsonism is the second most common movement disorder reported in patients with SLE. The age at onset is usually much earlier than in idiopathic Parkinson's disease (PD) and SLE patients more often exhibit other neuropsychiatric manifestations such as hallucinations, delirium, mutism, etc. [58]. Anti-dopaminergic antibodies have been detected in some of these patients, making possible that this disorder is within the spectrum of BG-encephalitis [62]. Other MDs identified in these patients include: cerebellar ataxia (Table 2), tremor, focal dystonia, tics, paroxysmal non-kinesigenic dyskinesia, and corticobasal-like syndrome [58]. However, a causal relationship with SLE or APS is not always well defined and it may be coincidental.

6. Autoimmune disorders with unclear etiology

6.1. Hashimoto's encephalopathy (SREAT)

Hashimoto's encephalopathy (HE) also known as “SREAT” is defined by the combination of neuropsychiatric symptoms, laboratory evidence of anti-thyroid antibodies and prominent clinical improvement with steroids along with lack of evidence of other disorders. Onset is usually between 45 and 55 years of age, and females are 5 times more commonly affected. Patients usually have high titers of anti-thyroid peroxidase antibodies; however, most patients are euthyroid or have subclinical hypothyroidism; overt hypothyroidism occurs in 20% of cases [63]. Antibodies reacting with the amino-terminal portion of α-enolase are detected in about 50% of cases. α-Enolase is a cytoplasmic glycolytic enzyme, but it is also present in the surface of several cell types, where it acts as a plasminogen receptor [64]. Antibodies against this enzyme have been detected in a number of disorders including SLE and multiple sclerosis; although their pathogenic role in HE and other disorders is uncertain [65]. MDs are observed in up to 80% of patients with HE, more commonly: tremor, myoclonus and gait ataxia; other reported MDs are chorea, and palatal myoclonus. Back-averaged EEG does not show a cortical correlate with myoclonus, suggesting a subcortical origin [63]. Presentations with prominent cerebellar ataxia and limbic encephalitis have also been described [66,67].

Pathological samples of patients with HE have demonstrated mild perivascular lymphocytic infiltration of small vessels. These vasculopathic changes have been related to stroke-like episodes and regional

hypoperfusion assessed with SPECT [68]. MRI is usually normal. Response to steroids is characteristic; improvement is usually observed within 4 to 6 weeks following treatment initiation. Replacement with thyroid hormones does not modify the course of the disease.

6.2. Opsoclonus-myoclonus syndrome

This disorder is characterized by chaotic, multidirectional, conjugate, saccades (opsoclonus). Myoclonus is one of the core features of OMS; it affects predominantly the limbs, but axial (craniocervical and trunk) myoclonus is not uncommon, other MDs such a gait ataxia and tremor are frequently observed. The disorder has a slight female preponderance, with bimodal peaks of age at presentation. In children, this disorder is commonly associated with neuroblastoma; in adults, however, it is associated with a wide variety of neoplasms such as breast or lung cancer and onconeuronal antibodies (particularly ANNA-2/Ri) and in some patients a parainfectious cause is assumed [69]. In a series of 114 patients, 61% of cases were considered idiopathic and 39% were paraneoplastic [70]. Neuronal surface antibodies were identified in only 11% of patients, mainly anti-GlyR in patients with lung cancer, but the frequency was not different compared to patients with lung cancer without OMS; however, 3 patients had antibodies directed to the novel cell surface epitope HNK-1 [70].

7. Paraneoplastic movement disorders

Cerebellar ataxia is the MD most commonly presenting as a classic paraneoplastic neurological syndrome (PNS) and is associated with a variety of antibodies including: ANNA-1 (anti-Hu), ANNA-2 (anti-Ri), PCA-1(anti-Yo), PCA-2, PCA-Tr, ZIC4, or the so-called "medusa head ataxia" antibodies; small-cell carcinoma of the lungs (SCLC) is the most commonly detected cancer [71]. These patients usually have a much rapid course than those with other forms of autoimmune cerebellar ataxia, with poor response to immunotherapy with worse prognosis [72].

Parkinsonism has been associated with Ma1/Ma2 antibodies, some of these patients may present with severe hypokinesia [73]. Most of these patients present with limbic, diencephalic or brain-stem encephalitis, frequently accompanied by supranuclear gaze palsy, sometimes evolving to complete ophthalmoplegia, REM-sleep behavior disorders, or narcolepsy; testicular germ-cell tumor is the most common underlying cancer [73]. Paraneoplastic chorea is most frequently associated with antibodies against CRMP5-IgG, followed by ANNA-1; these patients typically have comorbid polyneuropathy and other hyperkinesis such as dystonia and orobuccal dyskinesia [74]; SCLC is also the most common underlying cancer [75]. A paraneoplastic presentation of SPS is related to amphiphysin antibodies; they are identified in about 5% of patients with SPS, mainly in women with breast cancer [76]. Although, predominant upper limb rigidity has been reported in these patients [76], this feature has not been confirmed in other studies.

8. Clinical approach and diagnosis

An autoimmune pathogenesis should be suspected in patients with acute or subacute onset of MDs usually followed by rapid progression and accompanied neurological manifestations such as psychiatric manifestations, brainstem dysfunction, dysautonomia or frank encephalitis. Fluctuant neurological manifestations may be observed in patients with PERM; paroxysmal dizziness spells have been recently recognized in those with LGI1 antibodies [26], and "brainstem attacks" may precede the onset of GAD associated ataxia [54,77]. SPS on the other hand, has an insidious onset, and patients usually present with chronic evolution.

The phenomenology of the movements may be helpful to suspect an underlying autoimmune diagnosis. Onset of chorea or dyskinesia in children or young adults should raise suspicion of SC, NMDAR-encephalitis, SLE or APS. Facial dyskinesia has been typically related to NMDAR-encephalitis. In adults, autoimmune chorea is most frequently paraneoplastic; male gender, older age, severe chorea, comorbid peripheral neuropathy and weight loss increase the likelihood of cancer [78]. On the other hand, SLE and APS were the most frequent non-paraneoplastic causes in adults, whereas NMDAR-encephalitis is rare [78]. Cerebellar ataxia is the abnormal movement related to the widest variety of antibodies and autoimmune syndromes, therefore the approach of these patients may be oriented to testing a wide variety of antibodies; besides anti-GAD CA, where comorbid DM1 and other non-neurological autoimmune disorders may be a clue for diagnosis; there are few clinical clues orienting the underlying autoimmune process (Table 2). A group of IgG antibodies binding to the somatodendritic part of Purkinje cell located in the molecular lawyer of the cerebellum collectively known as "medusa head ataxia", although individually rare; they react with several antigens involved in the glutamate/calcium pathway: mGluR1, Homer-3, SJ/ITPR 1, CARP VIII, PKCγ, ARHGAP26, GluRδ2, DNER, VGCC, Nb/AP3B2, CDR2, and PCA-2 [79–81]. Underlying cancer is not uncommon and includes: SCLC; melanoma, liver cancer, and Hodgkin disease. Dystonia is not commonly reported in the context of autoimmune disease, but jaw dystonia and laryngospasm have been described in patients with ANNA-2 antibodies [82]. Limb dystonia may be observed in patients with NMDAR-encephalitis, BG-encephalitis, or SC. Autoimmune severe hypokinesis with other features of parkinsonism usually present with encephalopathy, either in patients with Ma1/Ma2 antibodies, anti-BG encephalitis or SLE. In a series of 10 patients, mean age 63.7 years, presenting with either multiple system atrophy, PSP or atypical parkinsonism were retrospectively identified, two patients had LGI1 antibodies and 8 had unidentified neuronal antibodies; intriguingly all patients had a remarkable clinical improvement with oral steroids [83]. The authors, however, did not provide information on how they suspected an autoimmune pathogenesis in these patients. An associated REM-sleep behavior disorder should raise suspicion of limbic encephalitis associated with VGKC-complex antibodies [84], anti-IgLON 5 or HE.

The clinician should keep in mind that there is no definitive neural antibody marker in some of these disorders, including SC, SLE or HE; therefore the diagnosis in many cases is suspected depending on the clinical context of each patient. Moreover, some antibodies are not readily available for commercial testing and are determined only in research laboratories (i.e. GlyR, HNK-1, etc.). In most cases, serum determination of antibodies is enough for diagnosis; however in patients with NMDAR-encephalitis testing of antibodies in the CSF may be necessary when negative results are obtained in the serum; in patients with GAD-associated autoimmunity, positive CSF antibodies may help to demonstrate intrathecal secretion and support a possible pathogenic role in patients with comorbid DM1 and low serum GAD antibodies. Positive non-neural antibodies such as anti-nuclear or anti-DNA antibodies are useful particularly in young women, when SLE is suspected; whereas anti-thyroid antibodies supports the diagnosis of HE in the appropriate clinical context, otherwise non-neural antibodies have a low diagnostic yield.

CSF in patients with autoimmune MDs may show mild pleocytosis, increased protein and positive oligoclonal bands, although these findings are not specific, they may help to support an autoimmune syndrome. MRI studies are usually unremarkable, except in patients with limbic and other encephalitis, where hyperintensities may be observed, particularly with VGKC-complex antibodies [85]. PET CT typically shows increased metabolism of basal ganglia or areas of inflammation detected on MRI [85]. In a recent study, ^{18}F-FDG PET/CT showed higher sensitivity than MRI to detect abnormalities in patients with autoimmune encephalitis, particularly lobar hypometabolism [86].

Suspicion of a paraneoplastic MD is based on age, gender, hereditary background, environmental risk factors and subacute onset. Some presentations such as NMDAR-encephalitis, OMS or Morvan's syndrome should raise suspicion of underlying neoplasm. The search for

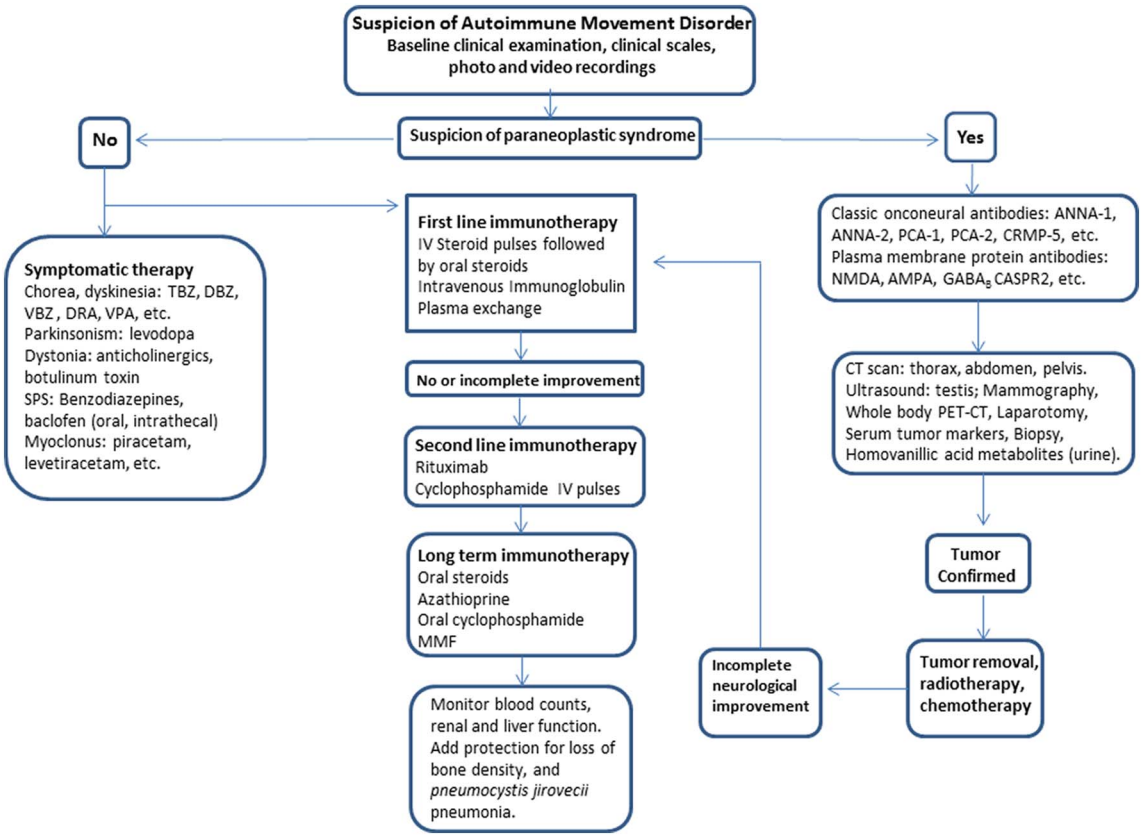

Fig. 2. Algorithm for diagnosis and treatment of autoimmune movement disorders.
DBZ: deutetrabenazine; DRA: dopamine receptor antagonists; MMF: mycophenolate mofetil; TBZ: tetrabenazine; VBZ valbenazine; VPA: valproic acid.

underlying cancer is more readily oriented when a panel of antibodies is obtained, SCLC, breast cancer, ovarian teratoma, testicular seminoma, neuroblastoma, and thymoma are the most commonly observed in the context of a paraneoplastic MDs (Fig. 2).

9. Therapy

Symptomatic therapy should be provided for most patients, the selection of pharmacology agents depends on the underlying phenomenology (Fig. 2 and Table 3). Treatment of an underlying cancer with tumor removal or chemotherapy may ameliorate the involuntary movements. Although this is less common in patients with onconeural antibodies, directed to intracellular proteins, where a prominent role of lymphocyte-T autoimmunity is present, tumor removal is of major importance in patients with ovarian teratoma and NMDAR-encephalitis.

Although some of these movement appear following an infection, antibiotic therapy is recommended only for patients with SC in order to provide secondary prevention for RF. Penicillin G benzathine intramuscular 1.2 million units every 21 days is recommended for patients that weight > 27 kg and 0.6 million units for those weighting < 27 kg until the age of 21 years; sulfa drugs can be used in case of allergy to penicillin [5]. Despite secondary prophylaxis, recurrence of SC may occur in up-to 40% of patients [87]. We discourage the use of immunotherapy in patients with sudden onset of tics, as PANDAS/PANS are controversial disorders.

Few patients may benefit from symptomatic therapy alone such as those with mild SC. However, steroids had been advocated for SC patients who develop side effects from neuroleptics and severe chorea [88], furthermore a randomized controlled trial of prednisone showed significant improvement in the duration and intensity of chorea [89]; benefit may also be observed in swallowing, chewing and language [90].

Most patients should receive immunotherapy, which may ameliorate the abnormal movements and associated neurological manifestations. High dose IV steroids followed by a course of oral prednisone; IV immunoglobulin (IVIg); and plasma exchange are considered first line therapy, failure to improve should lead to consider anti-CD20 therapy with rituximab or IV pulses of cyclophosphamide [91]. Although there are few randomized controlled trials of these drugs in patients with autoimmune MDs; IVIg showed improvement in stiffness and heightened-sensitivity scores in patients with SPS in a cross-over trial vs. placebo; where patients received each therapy for three months [92]. Benefit of IVIg was sustained for 6 weeks up to 1 year [92]. More recently a placebo-controlled trial of rituximab with 2 biweekly infusions of 1 g each in 24 patients with SPS showed no changes in the stiffness index at 6 months and improvements in quality of life were noted at 3 but not at 6 months, suggested a placebo effect, although a small proportion of patients on rituximab had meaningful improvements [93].

Long-term immunotherapy to keep remission and/or the use of drugs with steroid-sparing effect is considered for many patients in the long term. Immunotherapy is most effective for patients with autoimmunity related to plasma membrane antigens. Patients with a PNS associated with onconeural antibodies may also benefit from immunotherapy with steroids or cyclophosphamide, but the prognosis is usually worse. The duration of chronic immunotherapy is unknown, it has been suggested that medication withdrawal can be undertaken after 3–5 years without relapses or signs of active disease [91].

10. Conclusions

An autoimmune etiology is part of the differential diagnosis of practically the whole spectrum of MDs in patients of all ages and both genders, particularly when the course is acute or subacute. The

Table 3
Selected drug therapy for autoimmune movement disorders.

Drug class	Doses	Comments and side effects
Immunotherapy		
Immunoglobulins	IVIg 2 g/kg in 2–5 days every month	Doses can be administered on a monthly basis Acute SE: headache, fever, chest tightness, back pain, blood pressure changes, tachycardia, anaphylactic reactions (IgA deficient patients) Late SE: renal failure, thromboembolic events, hemolytic anemia
Steroids	Methylprednisolone 1 g IV for 3–5 days followed by prednisone 50–60 mg/day with progressive dose reduction	Monthly pulses of steroids are necessary in some conditions SE: hyperglycemia, hypertension, weight gain and osteoporosis. Add oral calcium 1500 mg/day, vitamin-D 1000 IU/day, sulpha, dapsone or pentamidine for *Pneumocystis jiroveci* prevention.
Plasma exchange	1.0–1.5 plasma volume per exchange	Invasive and time-consuming SE: hypotension, arrhythmias, infections, hemolysis
Anti-CD20	Rituximab 375 mg/m2 IV over 90 mins in 4 weekly doses or subcutaneous rituximab over 5–7 min	SE: Allergic infusion reactions (premedication is necessary), infections, neutropenia. B-cell count can be used as biomarker.
Intravenous immunosuppressive agents	Cyclophosphamide 750 mg/m2 IV	Monthly pulses of CF are necessary in some conditions SE: infections, ovarian failure, neutropenia, hemorrhagic cystitis
Oral immunosuppressive agents	Azathioprine 2–3 mg/kg/day, MMF 1.5–3.0 g/day in 2 doses	Target doses guided by the ALC. Measure TPMT activity for azathioprine (low activity increases the risk for SE) SE: fatigue, GI symptoms, myelo-toxicity, and liver toxicity.
Symptomatic therapy		
Dopamine depleters	Tetrabenazine 12.5 to 50 mg tid Deutetrabenazine 6, 9, 12 mg bid Valbenazine 40, 80 mg qd	Useful for several hyperkinetic MDs such as chorea or tics. Monitor for drug-induced sedation, insomnia, depression, akathisia, parkinsonism, no risk of tardive dyskinesia.
Antagonists of dopamine receptors	Risperidone 2–8 mg/day (oral)	Useful for several hyperkinetic MDs but only for < 2 weeks of treatment.
	Haloperidol 2–20 mg/day (IM)	Risk of acute dystonic reaction, TD, and drug-induced parkinsonism.
Muscle relaxants	Baclofen (oral) 10–60 mg/day or (intrathecal) 50–150 μg/day	Useful for stiffness and muscle spasms of SPS, PERM, etc. SE: drowsiness, dry mouth, ataxia, decreased cardiac output. Catheter dysfunction (intrathecal) may lead to severe withdrawal.
Benzodiazepines	Clonazepam 2.5 mg/day or Diazepam 5 mg/day (starting doses)	Useful for opsoclonus, myoclonus, stiffness and muscle spasms. SE: drowsiness, fatigue, ataxia, hypotonia, dry mouth.
GABAergic drugs	Gabapentin 300–900 mg tid Levetiracetam 500–100 mg bid Piracetam 7.2–24 g/day bid or tid	Useful for myoclonus, or muscle spasms SE: drowsiness, dizziness, ataxia, peripheral edema, or nervousness (with levetiracetam)
Anti-epileptics	Valproate 600–1800 mg/day Carbamazepine 200–1600 mg/day	Useful for Sydenham's chorea or myoclonus (valproate). Several SE, including ataxia, hyponatremia, liver toxicity, etc

ALC: absolute lymphocyte count; TD: tardive dyskinesia; TPMT: thiopurine methyl transferase; SE: side effects.
First line therapy include: IVIg, steroids, and PE, in case of poor response, escalation to rituximab or cyclophosphamide can be tried; maintenance therapy with oral prednisone/prednisolone with or without "steroid sparing agents": azathioprine or mofetil mychophenolate may be necessary.

phenomenological presentation of the MDs, along with associated neurological and medical manifestations, should be a diagnostic clue. In all the autoimmune MDs early recognition should rapidly lead to institution of treatment with immunosuppressive drugs and symptomatic therapy to improve the prognosis.

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Author roles

1) Research project: A. Conception, B. Organization, C. Execution;
2) Statistical Analysis: A. Design, B. Execution, C. Review and Critique;
3) Manuscript: A. Writing of the first draft, B. Review and Critique.
José Fidel Baizabal-Carvallo: 1A, 1B, 1C, 3A,3B.
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