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Narrative Review

Paraneoplastic movement disorders: phenomenology, diagnosis, and treatment

Martina Chirra[a,b], Luca Marsili[c,*], Simone Gallerini[d], Elizabeth G. Keeling[c], Roberto Marconi[d], Carlo Colosimo[e]

[a] Division of Hematology-Oncology, Department of Internal Medicine, University of Cincinnati, Cincinnati, OH, USA
[b] Department of Oncology, Medical Oncology Unit, University of Siena, Siena, Italy
[c] Gardner Family Center for Parkinson's Disease and Movement Disorders, Department of Neurology, University of Cincinnati, Cincinnati, OH, USA
[d] Unit of Neurology, Misericordia Hospital, Grosseto, Italy
[e] Department of Neurology, Santa Maria University Hospital, Terni, Italy

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ABSTRACT

Paraneoplastic syndromes include, by definition, any symptomatic and non-metastatic condition associated with a neoplasm. Paraneoplastic movement disorders are a heterogeneous group of syndromes encompassing both hyperkinetic and hypokinetic conditions, characterized by acute/sub-acute onset, rapidly progressive evolution, and multifocal localizations with several overlapping features. These movement disorders are immune-mediated, as shown by the rapid onset and by the presence of antineuronal antibodies in biological samples of patients, fundamental for the diagnosis. Antineuronal antibodies could be targeted against intracellular or neuronal surface antigens. Paraneoplastic movement disorders associated with anti-neuronal surface antigens antibodies respond more frequently to immunotherapy. The underlying tumors may be different, according to the clinical presentation, age, and gender of patients. Our search considered articles involving human subjects indexed in PubMed. Abstracts were independently reviewed for eligibility criteria by one author and validated by at least one additional author. In this review, we sought to critically reappraise the clinical features and the pathophysiological mechanisms of paraneoplastic movement disorders, focusing on diagnostic and therapeutic strategies. Our main aim is to make clinicians aware of paraneoplastic movement disorders, and to provide assistance in the early diagnosis and management of these rare but life-threatening conditions.

1. Introduction

Paraneoplastic neurological syndromes (PNS) include any symptomatic and non-metastatic neurological condition associated with a systemic neoplasm [1]. PNS affect 1–15% of cancer patients, with different prevalence according to the underlying tumor [2–4]. PNS might precede the diagnosis of the malignancy from 1 to 5 years in up to 70% of cases [5,6]. PNS pathogenesis is based on an immune response targeting antigens/epitopes shared by tumor cells and normal cells within the nervous system [7], differently from other non-neurological paraneoplastic syndromes in which the target antigen is found outside the central nervous system.

Abbreviations: AMPA-R, α-Amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid receptor; ANNA-3, antineuronal nuclear antibody 3; AP3B2/Nb, AP3B2/Nb Antibodies; PCA2, Purkinje cell cytoplasmic antibody type 2; CASPR2, contactin-associated protein 2; CRMP-5, collapsin-response mediated protein 5; CSF, cerebrospinal fluid; CT, computerized tomography; DPPX, dipeptidyl-peptidase-like protein 6; FDG, fluorodeoxyglucose; $GABA_{A/B}$-R, gamma-aminobutyric acid-$_{A/B}$ receptor; GAD, glutamic acid decarboxylase; GluRε2, GluR epsilon 2 antibodies; GQ1b, GQ1b ganglioside antibodies; GT1a, GT1a antibodies; HNK-1, human natural killer 1; Hu/ANNA-1, anti-neuronal nuclear antibody 1; i. v., intravenous; IgLON5, IgLON family member 5; LGI1, leucine-rich glioma inactivated 1; MRI, magnetic resonance imaging; NMDA-R, *N*-methyl-D-aspartate receptor; NSA, neuronal surface; NR2A, glutamate receptor NR2A antibodies; NR2B, glutamate receptor NR2B antibodies; NSCLC, non-small cell lung cancer; OMS, opsoclonus-myoclonus ataxia syndrome; PERM, progressive encephalitis with rigidity and myoclonus; PET, positron emission tomography; PMDs, paraneoplastic movement disorders; PNS, paraneoplastic neurological syndromes; Ri/ANNA-2, antineuronal nuclear antibody 2; SCLC, small cell lung cancer; SPS, stiff-person-syndrome; VGCC, voltage-gated calcium channels; TG, thyroglobulin antibodies; TPO, thyroid peroxidase; VGKC, voltage gated potassium channel

* Corresponding author at: Department of Neurology, University of Cincinnati, 260 Stetson Street, 45219, Cincinnati, OH, USA.
E-mail addresses: martina.chirra@gmail.com (M. Chirra), marsilla@ucmail.uc.edu (L. Marsili), keelineg@mail.uc.edu (E.G. Keeling), carlo.colosimo@uniroma1.it (C. Colosimo).

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Table 1
'Classic' paraneoplastic movement disorders, with the different underlying tumors, and antibodies typically found in association.

Paraneoplastic movement disorders	Neoplastic disease	Antibody
Opsoclonus-myoclonus ataxia syndrome	Breast cancer	Anti-Ri/ANNA-2 [16,17]; anti-glycine receptor [16].
	Lung cancer	Anti-glycine receptor [16]; anti-HNK-1 [16]; anti-kinesins [18]; anti-Zic2, anti-Zic4 [16,18]; anti-Ma2 [16]; anti-Hu/ANNA-1 [17]; anti-amphiphysin [17]; anti-GAD [19].
	Neuroblastoma	Anti-protein phosphatase-1 [18]; anti-Hu/ANNA-1 [18,20]; Anti-neuroblastoma and cerebellar structures [20].
	*Ovarian teratoma	*Anti-NMDA-R [16].
	**Testicular seminoma	**Anti-glycine receptor [16].
	Gastric cancer	Anti-Ma2 [16].
	Pyriform sinus cancer	Anti-GAD [21].
Paraneoplastic cerebellar degeneration	Breast cancer, gynecologic cancer, prostate cancer, upper gastrointestinal cancer	Anti-Yo [22–26].
	Hodgkin's Lymphoma	Anti-Tr [27].
	SCLC	Anti-VGCC [28–30]; anti-Hu/ANNA-1 [28–30]; anti-PCA2 [14]; anti-SOX-1 [29]; anti-CRMP-5 [31]; anti-ANNA-3 [32].
	NSCLC	Anti-Yo [33].
	Head and neck cancer	Anti-VGCC [34].

Onconeural antibodies: anti-Hu/ANNA-1, anti-Yo, anti-Ri/ANNA-2, ANNA-3, anti-CRMP-5, anti-amphiphysin, anti-GAD, anti-Ma2, anti-Tr, PCA2, SOX-1, and anti-Zic2/4. Neuronal surface antibodies: anti-NMDA-R, anti-glycine receptor, anti-LGI1, anti-HNK-1, anti-VGCC, anti-kinesins, anti-neuroblastoma and cerebellar structures, anti-protein phosphatase-1.

Paraneoplastic movement disorders (PMDs) are neurological conditions with either an excess (hyperkinetic) or paucity (hypokinetic) of movements, characterized by acute/sub-acute onset, rapid progression, and several overlapping features [8,9]. The etiopathogenesis of PMDs is immune-mediated. In presence of antibodies reacting against intracellular neuronal antigens, historically defined as onconeural antibodies (as in the 'classic' PMDs), the neuronal degeneration is due to cytotoxic T-cells [10–14]. These onconeural antibodies are considered markers of paraneoplastic disorders and do not have a direct pathogenic role. Differently, antibodies reacting against neuronal surface antigens (NSA) have a direct pathogenic role. NSA antibodies can recognize different extracellular structures, such as domains of receptors, ion channels, or components of neural plasma membranes.

We sought to describe the pathophysiological mechanisms and the clinical features of PMDs, focusing on the existing diagnostic strategies and therapeutic perspectives. Our main aims are to make internists, oncologists, and general neurologists aware of PMDs and to provide assistance to the early diagnosis and management of these rare but life-threatening conditions.

In this review, we considered articles involving human subjects published in English and indexed in PubMed between January 1992 and December 2018. Our MESH search terms included 'Paraneoplastic syndrome', 'Cancer', 'Malignancies', 'Antibodies', 'Onconeural antibodies', 'Neuronal surface antibodies', 'Opsoclonus-myoclonus', 'Paraneoplastic cerebellar degeneration', 'Autoimmune encephalitis', 'Limbic encephalitis', 'Anti-NMDA-R encephalitis', 'Paraneoplastic myoclonus', 'Paraneoplastic chorea', 'Paraneoplastic dystonia', 'Paraneoplastic tremor', 'Peripheral nerve hyperexcitability', 'PERM', 'Stiff person syndrome', 'Paraneoplastic parkinsonism'. No restrictions were applied to gender, age, ethnicity, disease duration, or disease severity. The reference lists were additionally screened for pertinent studies not included in the original searching strategy. Abstracts were independently reviewed for eligibility criteria by one author and validated by at least one additional author. Relevant articles were analyzed according to the following themes: 'Diagnosis and management of PMDs', and 'Tumors associated with PMDs'.

2. Paraneoplastic movement disorders

The clinical classification of PMDs is challenging because signs and symptoms frequently overlap across different disorders. The principal movement disorders that we will discuss in the present review are: opsoclonus (a series of involuntary multidirectional back-to-back saccades without an inter-saccadic interval), ataxia (altered muscle coordination), myoclonus (brief shock-like jerks lasting < 100 msec), chorea (irregular and purposeless movements, slower than myoclonus, that flit from one body part to another in a chaotic pattern), dyskinesia (any abnormal and involuntary movement showing characteristics that may overlap with chorea and also dystonia), dystonia (sustained or intermittent muscle contraction that causes abnormal movements or postures), tremor (rhythmic, oscillatory movement, due to the alternate activation of agonist and antagonist muscles), and parkinsonism (rigidity associated with bradykinesia, tremor, or postural instability). Other conditions that will be also discussed are neuromyotonia (inability to relax voluntary muscle after vigorous effort), myokymia (spontaneous, fine fascicular contractions of one or few muscles), and fasciculations (muscular twitching involving the simultaneous contraction of contiguous groups of muscle fibers) [15]. In this section, we describe the clinical features of PMDs and the type of tumors most commonly found in association. Each paragraph is organized and named according to the most important clinical feature of the associated syndrome, although many intersections exist (e.g., anti- *N*-methyl-D-aspartate receptor - NMDA-R - encephalitis is discussed under both encephalitis and dyskinesias, although the former is the most important condition found in association with those antibodies). First, we discuss the 'classic' PMDs, originally attributed to onconeural antibodies (Table 1). Then, we review the paraneoplastic autoimmune encephalitides, the associated antibodies (more frequently NSA antibodies) (Table 2) and the related movement disorders. Finally, a miscellaneous group of hyperkinetic and hypokinetic PMDs is considered (Table 3). However, the distinction between 'classic' and other PMDs, based on the positivity for onconeural or NSA antibodies respectively, appears to be less strict since 'classic' PMDs are also associated with NSA antibodies and vice versa.

3. Classic paraneoplastic movement disorders

3.1. Opsoclonus-myoclonus ataxia syndrome

Opsoclonus-myoclonus ataxia syndrome (OMS) is a peculiar syndrome characterized by opsoclonus accompanied by myoclonic jerks in the limbs or trunk, ataxia, tremor, and encephalopathy [16,54]. It can occur in both pediatric and adult patients, although the origin is different according to the age of the patient. In children, paraneoplastic OMS occurs in association with neuroblastoma in almost 50% of cases [20], whereas in adults the causes of OMS are mostly infectious, toxic-

Table 2
Paraneoplastic autoimmune encephalitides, with the different underlying tumors, and antibodies typically found in association.

Paraneoplastic movement disorders	Neoplastic disease	Antibody
Autoimmune encephalitides	Ovarian teratoma (rare: extra-ovarian teratoma, ovarian cancer)	Anti-NMDA-R [35,36]; anti AMPA-R [37].
	§Thymus carcinoma	§Anti-NMDA-R [36]
	#Thymomas	#Anti-LGI1 [35]; anti-CASPR2 [38]; anti-AMPA-R [37]; anti-$GABA_A$-R [39,40]; anti-GAD [39]; anti-CRMP-5 [31].
	Testicular cancer	Anti-NMDA-R [36]; Anti-Ma2 [35,41].
	Pancreatic cancer	Anti-NMDA-R [36].
	Lung cancer	Anti-NMDA-R [36]; anti-Ma2 [42]; anti-AMPA-R [37]; anti-$GABA_B$-R [39,43]; anti-Hu/ANNA-1 [1]; anti-CRMP-5 [31]; anti-amphiphysin [44].
	Breast cancer	Anti-NMDA-R [36]; anti-Ma2 [45]; anti-AMPA-R [37]; anti-amphiphysin [44].

Onconeural antibodies: anti-Hu/ANNA-1, anti-CRMP-5, anti-amphiphysin, anti-GAD, anti-Ma2. Neuronal surface antibodies: anti-NMDA-R, anti-AMPA-R, anti-$GABA_{A/B}$-R, anti-CASPR2, anti-LGI1.

metabolic, and lastly, paraneoplastic. In adults, paraneoplastic OMS occurs in association with small cell lung cancer (SCLC), ovarian cancer, and breast cancer [16,55]; exceptional cases have been linked to other tumors such as gastric cancer [16,56] and non-Hodgkin lymphomas [57] (Table 1). The search for antibodies related to OMS has not revealed a specific biomarker of the disease. So far, the most significant associations observed are as follows: anti-Ri/ANNA-2 antibodies in patients affected by paraneoplastic OMS and breast cancer [16,55]; and anti-glycine receptor NSA antibodies in patients affected by paraneoplastic OMS and lung cancer [16]. Finally, Armanguè et al. [16], have recently described new NSA antibodies against the epitope named human natural killer 1 (HNK-1) in patients with paraneoplastic OMS and lung cancer.

3.2. Paraneoplastic cerebellar degeneration

Paraneoplastic cerebellar degeneration is considered one of the most common paraneoplastic neurological presentations of tumors in general. The most frequently involved tumors in paraneoplastic cerebellar degeneration are SCLC, breast and gynecological cancers, prostatic cancer, and Hodgkin's lymphoma, although sporadic cases of non-Hodgkin's lymphoma and gastric cancers have also been described [28,58–60]. Clinical features may include ataxia of gait and limbs, diplopia, dysarthria, and dysphagia, reaching a plateau within 6 months. In some cases, blurry vision, nystagmus, and opsoclonus are recorded as well [31,58]. Magnetic resonance imaging (MRI) is usually normal during the initial stages of paraneoplastic cerebellar degeneration, whereas over time cerebellar atrophy becomes evident. Paraneoplastic cerebellar degeneration needs to be differentiated from other rapidly progressing acquired cerebellar ataxias, including but not limited to infectious and toxic ataxias, autoimmune ataxias (e.g., associated with diabetes type 1 and thyroid disease, usually displaying anti-glutamic acid decarboxylase – GAD – antibodies; see encephalitides), and vitamin B deficiency-related ataxias. From a pathological point of view, the hallmark of paraneoplastic cerebellar degeneration is a widespread degeneration of Purkinje cells, accredited to inflammatory infiltrates [61,62]. Both onconeural and NSA antibodies have been described in association with paraneoplastic cerebellar degeneration. Anti-Yo antibodies are the most frequently found in this condition, whereas anti-Tr antibodies are observed less commonly. Anti-Yo antibodies are mainly related to gynecological or breast cancers, followed by gastrointestinal and prostate cancers [23,26,63,64], anti-Tr antibodies are associated with Hodgkin's lymphoma [27]. Forty per cent of patients with SCLC develop NSA antibodies in conjunction with paraneoplastic cerebellar degeneration, namely antibodies against voltage-gated calcium channels (VGCC) (in this case, a Lambert-Eaton myasthenic syndrome could be associated); 20% of them develop anti-Hu/ANNA-1 antibodies, and a minority of cases, develop antibodies anti-collapsin-response mediated protein 5 (CRMP-5), anti-amphiphysin, anti-Purkinje cell cytoplasmic antibody type 2 (PCA2), and anti-ANNA-3 [14,30–32] (Table 1). The largest group of patients with paraneoplastic cerebellar degeneration without identifiable antibodies comprises those affected by non-small cell lung cancer (NSCLC) followed by other conditions such as glottal-pharyngeal cancers [65] and chronic lymphatic leukemia [Marsili et al., personal oral communication 2014].

4. Paraneoplastic autoimmune encephalitides and associated movement disorders

Autoimmune encephalitides (also called limbic encephalitides when involving the limbic system) are a heterogeneous group of conditions characterized by acute to sub-acute onset, rapid progression (usually < 6 weeks), deficits of memory and cognition, and association with different movement disorders [66]. Autoimmune encephalitis may be the expression of infectious conditions, autoimmune disorders (e.g., lupus, acute disseminated encephalomyelitis), or paraneoplastic

Table 3
Main hyperkinetic and hypokinetic paraneoplastic movement disorders, with the different underlying tumors, and antibodies typically found in association.

Paraneoplastic movement disorders	Neoplastic disease	Antibody
Myoclonus	Lung cancer, breast cancer, melanoma	Anti-amphiphysin [3]
Chorea	Lung cancer, thymomas	Anti-CRMP-5 [46]; anti-Hu/ANNA-1 [47,48]; anti-$GABA_A$-R, anti-NMDA-R [49].
	Non-Hodgkin lymphoma	Anti-CRMP-5 [46].
	Head and neck cancer	Anti-CRMP-5 [46].
	Ovarian teratoma	Anti-NMDA-R [49].
Dystonia	Breast cancer	Anti-Ri/ANNA-2 [50].
	Ovarian teratoma	Anti-NMDA-R [50].
Paraneoplastic parkinsonism	Testicular cancer	Anti-Ma2 [51].
	Ovarian teratoma	Anti-NMDA-R [49].
Peripheral nerve hyperexcitability	Lung cancer	Anti-CRMP-5 [52].
Stiff person syndrome	Breast cancer, Lung cancer, thymoma	Anti-amphiphysin [3]; anti-glycine receptor [53]; $GABA_A$-R [49]; Anti-Ri/ANNA-2 [49].
	Lymphoma	Anti-DPPX [49].

Onconeural antibodies: anti-Hu/ANNA-1, anti-Ri/ANNA-2, anti-CRMP-5, anti-amphiphysin, anti-Ma2. Neuronal surface antibodies: anti-glycine receptor, anti-VGKC.

disorders, exhibiting diverse immunologic associations, clinical manifestations, and finally therapeutic outcomes. In this section, we will discuss paraneoplastic autoimmune encephalitides, according to their underlying antibodies, given that each one of these antibodies is associated with different epidemiological and clinical features (Table 2). We will then focus on the description of the main movement disorders associated with each condition.

4.1. Anti-NMDA-R encephalitis

Anti-NMDA-R encephalitis, predominant in females (F:M ratio 4:1), probably represents the most common autoimmune encephalitis subtype worldwide [67]. It may be due to both paraneoplastic and non-paraneoplastic conditions (e.g., Herpes-simplex virus-associated encephalitis) according to different demographic and ethnic features [68]. The most prevalent underlying tumor is ovarian teratoma (94%), followed by extra-ovarian teratomas (in women), lung, breast, testis (in men), thymus, pancreas, and other ovarian cancers. All these tumors, except for ovarian teratoma, are predominant in adult patients (> 50 years old); Asians and African-Americans are more susceptible to develop those tumors (40–50%) compared to Caucasians or Hispanics (~30%). Young men and children show a much lower prevalence of paraneoplastic anti-NMDA-R encephalitis (6%); in that population, non-paraneoplastic forms are more frequent [36,67]. Prodromal symptoms consist of behavioral abnormalities, mood disturbances, and psychosis (e.g., hallucinations, delusions). The prodromal phase is followed by an acute phase consisting of severe psychiatric positive symptoms, high fever, seizures (with the typical EEG pattern named 'extreme delta brush activity') [69], status epilepticus, and hyperkinetic movements (opisthotonus, chorea, tremor, oculogyric crisis, orofacial and limb dyskinesias, stereotypies, and ataxia), followed by hypokinetic phenomena (general rigidity/parkinsonism, or catatonia) [70]. At this stage, autonomic failure and hypoventilation requires admission to intensive care units and continuous monitoring of vital signs. The disease course is generally prolonged (months) and insidious with possible relapses. Anti-NMDA-R antibodies are usually detected in cerebrospinal fluid (CSF) or serum, and a follow-up of antibodies titer is helpful to monitor the prognosis.

4.2. Other paraneoplastic autoimmune encephalitides

Other paraneoplastic autoimmune encephalitides, not anti-NMDA-R-mediated, include both NSA antibodies and onconeural-mediated autoimmune encephalitides. The first group consists of anti-leucine-rich glioma inactivated 1 (LGI1), anti-contactin-associated protein 2 (CASPR2), anti- a-amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid receptor (AMPA-R), and anti-gamma-aminobutyric acid-$_{A/B}$ receptor ($GABA_{A/B}$-R) associated encephalitides. The second group comprises anti-GAD, anti-Ma-2, anti-Hu/ANNA-1, anti-CRMP-5, and finally anti-amphiphysin associated encephalitides.

LGI1 encephalitis is rarely associated with tumors (~10% of cases) when compared to other paraneoplastic autoimmune encephalitides, the most frequent condition in which it occurs being thymoma [34,70]. However, out of NSA antibodies, LGI1 are most frequently found in patients with limbic encephalitis [71,[72]]. Usually, men older than 50 are the most affected population in paraneoplastic LGI1 limbic encephalitis. Movement disorders associated with LGI1 limbic encephalitis are the so-called faciobrachial dystonic seizures, described in 40% of cases, and consisting of focal epileptic seizures associated with paroxysmal dystonic/dyskinetic movements that occur on facial and arm muscles, often alternating from one side to another [73,74]. Autonomic symptoms (e.g., diarrhea, sialorrhea, hyperthermia, blood pressure fluctuations, tachycardia/bradycardia) are present in about 10% of patients [75], occasionally occurring alongside neuromyotonia [49].

Anti-CASPR2 encephalitis is associated with thymoma and other tumors in a variable percentage ranging from 10 to 40% of reported cases [38]. Anti-CASPR2 encephalitis might associate with dysautonomia and peripheral nerve hyperexcitability (e.g., Morvan's syndrome, see peripheral nerve hyperexcitability), or with choreic movements.

Anti-AMPA-R encephalitis typically presents with memory loss and confusion, possibly associated with dyskinesia, or parkinsonism [37]. Anti-AMPA-R encephalitis is predominant in females, and underlying tumors have been found in ~65% of reported cases, namely (in order of frequency) SCLC, thymoma, breast cancer, ovarian teratoma, and finally other lung cancers [37].

Anti-$GABA_A$-R encephalitis is characterized by seizure and rapidly progressive status epilepticus with the possibility of associated movement disorders such as chorea, dystonia, OMS, and stiff person syndrome (SPS) [40]. Thymoma is the most frequently associated tumor (25% of cases) [39]. Anti-$GABA_B$-R encephalitis, characterized by memory loss and seizures, might be associated (although infrequently) with movement disorders such as orolingual dyskinesia [43]. Underlying associated tumors are SCLC (50% of reported cases) [39].

Anti-GAD encephalitis is rarely paraneoplastic, and when present the underlying tumor is usually a thymoma [39]. When other antibodies are present along with Anti-GAD, the possibility of a paraneoplastic diagnosis increases [76]. Anti-GAD encephalitis might manifest as late onset cerebellar degeneration, temporal lobe epilepsy, or limbic encephalitis associated with SPS.

Anti-Ma2 encephalitis may affect the limbic system, the hypothalamus, and the brainstem individually or in combination with one another [77]. Therefore, the presenting symptoms can originate in any of these regions, followed by progression to the others. In fact, some patients may show sleep disturbances (e.g., daytime sleepiness, narcolepsy, REM-sleep abnormalities), hyperphagia, and hypothalamic or pituitary hormonal deficits in addition to limbic dysfunction [1]. In other cases, hypokinetic movement, supranuclear vertical gaze palsy [78] or even jaw dystonia are evident [1]. Whenever there are abnormal facial movements and ocular abnormalities, Whipple's disease should be considered [79]. Differently, when sleep disorders, ocular movement abnormalities, and parkinsonism are present, it is also important to rule out the IgLON5-related tauopathy, a non-paraneoplastic autoimmune movement disorder [49]. Both cerebellar symptoms and peripheral neuropathy occur rarely [42,80]. In young men (< 50 years old), anti-Ma2 encephalitis is usually associated with testicular germ-cell tumors [35,41]; in older men and women (> 50 years old), however, the most common tumors are non-SCLC and breast cancer [35,42]. anti-Hu/ANNA-1 encephalitis is characterized by seizures involving the extremities or tongue, and/or status epilepticus. The underlying tumor is usually SCLC [1].

Anti-CRMP-5 encephalitis is an encephalomyelitis associated with sensorimotor neuropathy, cerebellar ataxia, and chorea [1]. The underlying tumors are usually SCLC and thymoma. [31]. Anti-amphiphysin encephalitis is characterized by rigidity (possibly configuring SPS), confusion, spasms, and memory loss. Main associated tumors are SCLC (90% of reported cases) and breast cancer [44].

5. Hyperkinetic conditions

5.1. Myoclonus

The 'classic' PNS myoclonic disorder is OMS, characterized by myoclonic movements of limb and trunk [17]. Myoclonic jerks might be observed also within the context of encephalitic syndromes, as in the LGI1 limbic encephalitis. However, as mentioned before, myoclonus can also occur as a presenting isolated feature of a PMD. In patients with anti-amphiphysin antibodies, myoclonus can involve the diaphragm, spine, or limbs and may be associated with other movement disorders, namely tremor, chorea, dystonia, and rigidity [2]. In anti-amphiphysin-associated myoclonus, the most common causative tumors are lung (~60%), breast (~30%), and melanoma (~5%),

(Table 3). Myoclonus has been associated with thyroid carcinoma, although no specific antibodies have been identified within this relationship [81]. In addition, myoclonus has been linked to anti-Ri/ANNA-2 antibodies, but without any evidence of underlying cancers [82].

5.2. Chorea

There are a wide number of causes of chorea ranging from primary (genetic such as Huntington's disease) to secondary. Secondary causes include structural lesions (e.g., vascular, oncological, inflammatory), drugs (e.g., neuroleptics), and toxic-metabolic disorders. Choreic symptoms, when associated with other peripheral (polyneuropathy) or central (encephalitis, psychiatric disturbances, or cerebellar ataxia) neurological conditions may configure PMDs. Paraneoplastic chorea is a rare condition and is therefore infrequently considered among the differential diagnosis of these hyperkinetic disorders. In paraneoplastic chorea, brain MRI often shows bilateral hyperintensity of caudate nuclei and putamen [57]. Paraneoplastic chorea has been described in association with different antibodies in the following order of frequency: anti-CRMP-5, anti-Hu/ANNA-1, anti-CASPR2, and anti-LGI1, the latter two being found mostly in association with non-paraneoplastic-(autoimmune)-chorea [46,47]. Finally, paraneoplastic chorea may be seen in the spectrum of involuntary movements in several paraneoplastic autoimmune encephalitides (see related section). Anti-CRMP-5 antibodies are associated respectively with SCLC in 70% and thymoma in 30% of diagnosed cases [31,48]. Rarely, anti-CRMP-5 antibodies have been associated with non-Hodgkin lymphoma and tonsillar cell carcinoma. Other tumors reported alongside paraneoplastic choreas are chronic myeloid leukemia, Hodgkin lymphoma, and also breast, renal, and prostate carcinoma [46,47]. Even so, autoantibodies remain unidentified in > 50% of paraneoplastic choreas [57]. For further antibodies associated with paraneoplastic chorea, see Table 3. Finally, orofacial dyskinesia are choreic movements characteristic of anti-NMDA-R encephalitis [11,36], however they may be found in severe encephalitis (e.g., confusion, decreased level of consciousness, seizures, myoclonus) when associated with neurexin-3α antibodies [83,84]. Only few patients have been reported to date, and no tumors have been detected. While some patients partially improved with immunotherapy, others had no benefits and showed a rapidly progressive deterioration [84].

5.3. Dystonia and tremor

Paraneoplastic dystonia is typical of patients with brainstem encephalitis within the context of anti-Ri/ANNA-2 antibodies and is associated with breast cancer [3]. In some cases, other types of dystonia, namely axial/neck dystonia, and laryngospasm are present. Uniquely, limb dystonia may be associated with pediatric anti-NMDA-R encephalitis (Table 3) [85].

Tremor can be present in encephalopathic conditions when associated with anti-LGI1, anti-CASPR2, anti-NMDA-R, and anti-dipeptidyl-peptidase-like protein 6 (DPPX) antibodies (in this last case myoclonus and dysautonomia are characteristic symptoms) [49,76,85–88]. Anti-DPPX antibodies are found in lymphomas in < 10% of cases [39]. Different types of tremor may be observed: intention and action tremor can occur in various paraneoplastic cerebellar degenerations, whereas Holmes tremor (e.g., an irregular 3–4 Hz tremor, present at rest and exacerbated with posture and action) is typically associated with paraneoplastic cerebellar degeneration and anti-Yo antibodies [58].

6. Hypokinetic conditions

6.1. Paraneoplastic parkinsonian syndromes

Paraneoplastic parkinsonian syndromes are uncommon conditions, typically associated with encephalomyelitis and involving the brainstem in nearly 50% of cases [42,89]. Vertical gaze palsy is common (~60% of cases), resembling the atypical parkinsonian syndrome 'progressive supranuclear palsy' [90]. Hypokinesia, rigidity, blepharospasm, and reduced verbal fluency are also frequently reported [42,51,78,89]. An autonomic dysfunction characterized by hypoventilation and hyperthermia, associated with facial grimacing, abdominal contractions, and dystonia, might present as a complication [91]. Underlying tumors are most commonly B-cell lymphoma [92], lung carcinoma [93] possibly in association with anti-CRMP-5 antibodies [52], and finally testicular tumors in young males presenting with anti-Ma2-associated encephalitis (see anti-NMDA-R encephalitis) (Table 3) [51].

7. Other conditions

7.1. Stiff-person syndrome

Stiff person syndrome (SPS) is a disease spectrum characterized by slowly progressive axial rigidity associated with intermittent painful spasms. SPS, prevalent in females, may be idiopathic or secondary to autoimmune disorders or paraneoplastic conditions (5% of cases). Some variants of this condition include stiff limb syndrome, jerking stiff person syndrome, and progressive encephalitis with rigidity and myoclonus (PERM) [89,94]. SPS is a fluctuating condition, improving during sleep but exacerbated by movements, sensory stimulation, or different emotions [89]. Spasms and myoclonic jerks may present as well. Anti-GAD autoantibodies are found in 50–90% of SPS cases; other antibodies found in association with SPS are anti-amphiphysin and anti-glycine receptor. Anti-GAD SPS is mostly due to autoimmune diseases (e.g., diabetes type 1), whereas anti-amphiphysin and anti-glycine receptor SPS are frequently associated with solid tumors [3,53,89]. Paraneoplastic SPS typically affects both limbs and may be associated with sensory neuronopathy. Anti-glycine receptor antibodies are known to have false positives outside the phenotype of SPS and PERM (e.g., it has been reported in optic neuritis and epilepsy) [49]. Lastly, anti-amphiphysin antibodies may also be found in PERM [89,95], a condition characterized by altered consciousness, brainstem manifestations, myoclonus, cerebellar ataxia, and diffuse rigidity (Table 3) [96].

7.2. Peripheral nerve hyperexcitability

Peripheral nerve hyperexcitability includes by definition a number of different conditions such as neuromyotonia, myokymia, or fasciculations, characterized by spontaneous muscle activity and motor nerve hyperexcitability [15]; however only neuromyotonia (isolated or in the context of Morvan's syndrome) may be paraneoplastic. They are included in this review as they may be confused with movement disorders and are therefore worth keeping in mind in the differential diagnosis. Peripheral nerve hyperexcitability may be associated with anti-voltage gated potassium channel antibodies (VGKC) in up to 40% of cases, with 25% of these due to PNS [89]. Other antibodies found in association with peripheral nerve hyperexcitability are anti-CASPR2, either in isolated neuromyotonia or as part of Morvan's syndrome (e.g., neuromyotonia accompanied by psychiatric symptoms) [38,97]. Finally, anti-LGI1 antibodies and anti-contactin 2 antibodies have also been identified in patients with peripheral nerve hyperexcitability [49,74,98].

8. Differential diagnosis and diagnostic algorithm

Initially, clinicians should be able to detect the presence of hyper-/hypokinetic movement disorders in their patients, to describe their phenomenology (isolated or combined tremor, myoclonus, ataxia, dystonia, parkinsonism, etc.), and then to verify their acute/sub-acute modality of onset. When dealing with complex conditions, it could be helpful to involve also a consultant neurologist expert in movement disorders. Ideally, it should be taken into account that PMDs only rarely

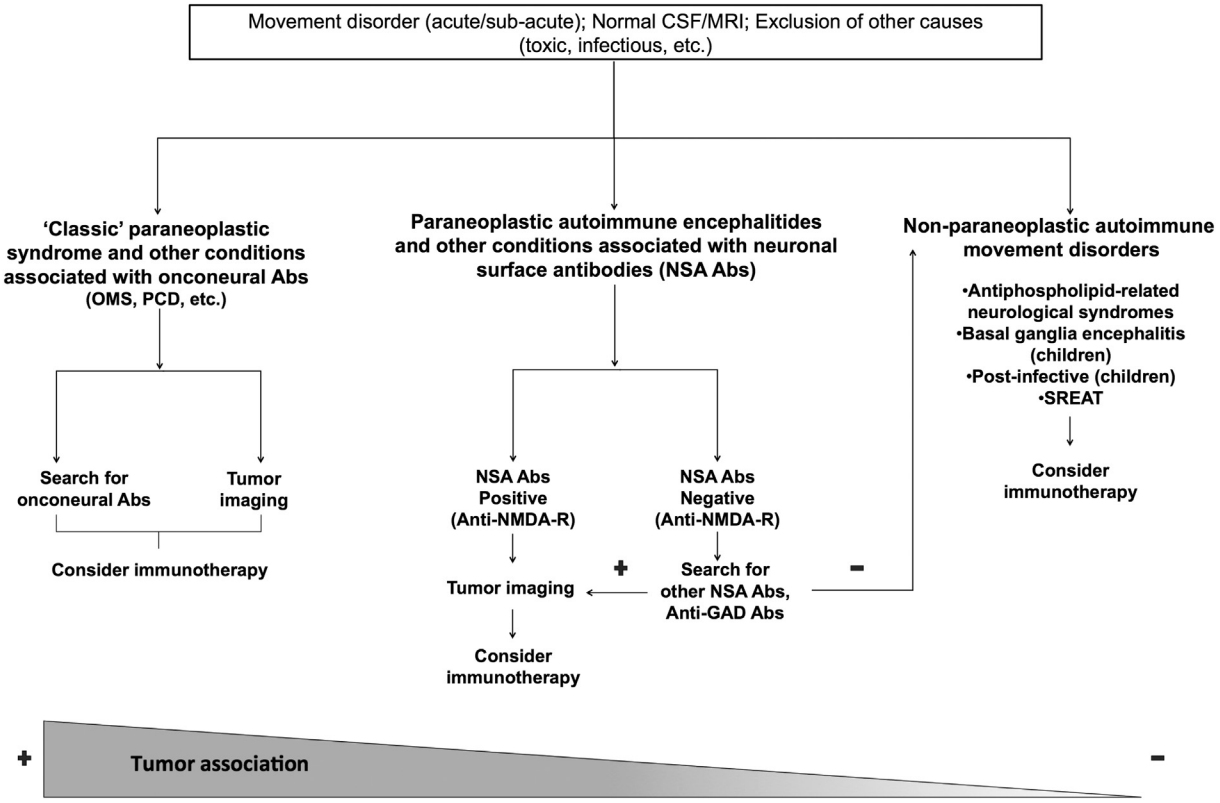

Fig. 1. Flow-chart of the diagnostic-therapeutic algorithm proposed for paraneoplastic movement disorders (PMDs).
Once secondary causes have been ruled out, clinicians should consider, according to the clinical presentation: 'classic' paraneoplastic syndromes and other conditions associated with onconeural antibodies, autoimmune encephalitides and other conditions associated with neuronal surface antibodies, and finally other immune disorders. The goal is the diagnosis and treatment of the underlying tumor when possible, and immunotherapy when necessary. Contemporarily, the examination of possible tumor-associated antibodies is helpful to achieve a correct diagnosis and a possible prognosis. As shown in the lower part of the figure (Grey triangle), the likelihood for a tumor to be the underlying cause of the movement disorder is higher for conditions associated with onconeural antibodies compared to conditions associated with neuronal surface antibodies. CSF, cerebrospinal fluid; MRI, magnetic resonance imaging; Abs, antibodies; OMS, opsoclonus-myoclonus ataxia syndrome; PCD, paraneoplastic cerebellar degeneration; NSA, neuronal surface; NMDA-R, *N*-methyl-D-aspartate receptor; GAD, glutamic acid decarboxylase; SREAT, steroid responsive encephalopathy associated with autoimmune thyroiditis.

present as isolated conditions, whereas they are typically seen in the context of a more generalized disorder (e.g., encephalitis, other neurological and psychiatric symptoms, etc.) and/or with associated warning signs such as rapid progression, constitutional symptoms, or a systemic neoplasm. In this case, it is necessary to proceed with a thorough examination, which implies neuroimaging and CSF analysis. In case of negative neuroimaging results (except for limbic encephalitis in which bilateral T2/FLAIR hyperintensity in medial temporal lobes is a common feature), or aspecific CSF inflammatory pattern (e.g., lymphocytic pleocytosis, increased protein concentration, elevated IgG index, and oligoclonal bands), it is important to rule out common causes of other secondary movement disorders (e.g., infections, tumor, stroke, drug-induced, metabolic, endocrinological conditions, etc.), and then to consider a possible immune-mediated etiopathogenesis (Fig. 1). Hence, three different scenarios are possible: (a) PMDs associated with onconeural antibodies ('Classic' PMDs, and other conditions); (b) PMDs associated with NSA antibodies (paraneoplastic autoimmune encephalitides and other conditions); or (c) other non-paraneoplastic autoimmune movement disorders. About 80% of patients with PNS have positive diagnostic screenings for cancer upon initial assessment. Tumors might be identified with computerized tomography (CT) imaging (chest, abdomen, brain), fluorodeoxyglucose (FDG)- positron emission tomography (PET), or both [99–101]. In some specific conditions such as microscopic intratubular germ cell testicular neoplasms, imaging could be negative and tumors are only revealed by bioptic exams [41]. The search for paraneoplastic antibodies (onconeural and NSA antibodies) might be time-consuming and highly expensive, especially considering that many cases do not reach a definite diagnostic confirmation. Due to overlapping syndromes, in some cases, the search for onconeural anti- bodies (in the common clinical practice, anti-Hu/ANNA-1, Anti-Ri/ANNA-2, and anti-Yo antibodies on serum samples) can be combined with the search for NSA antibodies (for instance, anti-NMDA-R antibodies, possibly followed by other classes of NSA antibodies both on serum and CSF samples) [102]. To help resolve some of these issues, specific diagnostic criteria have been proposed [6]. However, when dealing with symptoms typically associated with 'classic' PMDs syndromes, it is important to intensify tumor and antibody screening, given their high association with underlying tumors. In general, if primary screening is negative, it is recommended to repeat screening after 3–6 months and then subsequently every 6 months for up to 4–5 years [100], although some differences exist. For example, a patient with anti-Hu/ANNA-1 antibodies should be tested every 3–6 months for 3 years, whereas a patient with anti-LGI1 antibodies requires only a one-time screening (given that it rarely associates with neoplastic conditions). Together with systemic or surgical tumor treatment, immunotherapy should be considered to improve neurological symptoms. Among PMDs associated with NSA antibodies, anti-NMDA-R encephalitis is the most common and should be tested first. In case of positive results, it is recommended to screen for the underlying tumors; in case of negative testing, it is suggested to test for other related antibodies (e.g., anti-LGI1, anti-CASPR-2, etc.) according to the specific clinical presentation (Table 2). In general, serological testing is recommended to optimally test for some antibodies, including but not limited to anti-LGI1, anti-CASPR-2, and anti-GAD antibodies, whereas

Table 4
Non-paraneoplastic immune-mediated conditions and related clinical-serological features.

Syndrome	Movement disorders and main clinical features	Antibody
Antiphospholipid syndrome	Chorea (Most frequent)	Anti-cardiolipin; lupus anticoagulant; anti-b2-glycoprotein [104–106].
Basal ganglia encephalitis (childhood)	Parkinsonism, dystonia, chorea and psychiatric features	Anti-dopamine D2 receptor [107].
Steroid responsive encephalopathy associated with autoimmune thyroiditis (SREAT)	Ataxia, myoclonus, encephalitis	Anti-TPO; anti-TG [108,109].
Post-infectious (childhood)	Ataxia, choreoathetosis (Post-viral encephalitis)	Anti-$GABA_AR$; anti-NMDAR [110,111].
	Sydenham's chorea (Post group A streptococcal infection)	Anti-GM1 [112]; anti-tubulin [112]; anti-neuronal glycolytic enzymes [113]; anti-dopamine D1 receptor and anti-dopamine D2 receptor [107,114].
Miscellaneous	Parkinsonism, ataxia, chorea, sleep disorders and bulbar symptoms	Anti-IgLON5 [83,115,116].
	Atypical Miller-Fisher syndrome (Ataxia, areflexia, ophthalmoplegia, psychosis and involuntary movements)	Anti-GQ1b; anti-GT1a; anti-GluRε2 and anti-glutamate NR2B- and NR2A-containing heteromers of NMDAR [117].
	Cerebellar ataxia	Anti-Homer-3 [118,119]; anti- AP3B2/Nb [120]; anti-GAD [48].

some others are primarily found in CSF (e.g., anti-glycine receptor or anti-NMDA-R antibodies) [49,96,103]. Even before obtaining the results of the antibody assay, early immunotherapy is strongly suggested, and whenever this therapeutic approach fails, a second line immunotherapy could be considered. Finally, in the differential diagnosis, other autoimmune movement disorders, namely antiphospholipid–related neurological syndromes, post-infective chorea (e.g., Sydenham's chorea and basal ganglia encephalitis in children), and then miscellaneous other autoimmune and infective conditions (mycoplasma pneumoniae, varicella zoster virus, Epstein-Barr virus, enterovirus) should be taken into account (Table 4).

9. Therapeutic perspectives

The first step in PMDs therapy is the oncological treatment of the underlying tumor, when diagnosed, and the administration of drugs acting on the immune system, when necessary. Patients with testicular germ-cell tumors and anti-Ma2 encephalitis, for example, usually benefit from orchiectomy followed by steroid therapy, with an average of ~35% of cases responsive to treatment [63]. Paraneoplastic choreas, on the other hand, tend to have a bad prognosis (except for paraneoplastic choreas associated with LGI1 and CASPR2 antibodies) [121]. Drugs acting on the immune system consist of first and second line treatments. As first line treatments, intravenous (i.v.) steroids (Methylprednisolone 1 g i.v. for 2–5 days followed by gradual tapering; monthly administrations might be required), i.v. high-dose immunoglobulins (0.4 g/Kg/day for 2–5 days; monthly administrations might be required), and plasma-exchange (variable volumes might be exchanged) should be considered [122]. As second line treatments, different immunosuppressive agents can be employed, namely Azathioprine (2–3 mg/Kg/day; it might be used chronically) and Cyclosporine (7–14 mg/Kg/day for 1–2 weeks, followed by gradual tapering). Last but not least, Rituximab (a monoclonal antibody that targets the CD20 receptor on the surface of B cells) (375 mg/m^2 in acute i. v. administration, followed by subcutaneous weekly administrations) and Cyclophosphamide (an alkylating agent that cross-links DNA) (750 mg/m^2 i. v.; monthly administrations might be required) have occasionally been used as off-label second line treatments. In any case, a multidisciplinary approach involving both neurologist and oncologist is strongly recommended. In fact, several PMDs, in particular those associated with NSA antibodies, tend to relapse after the first line treatments, thus requiring an intensive oncological follow-up and a neurological evaluation at the recurrence for possible second-line treatments (officially approved or off-label) [102]. In general, onconeural antibodies are strongly associated with an underlying tumor compared to NSA antibodies, being predictors of scarce response to immunotherapy [49]. Finally, symptomatic therapy varies according to the different underlying neurological symptoms. For example, paraneoplastic-dystonias benefit from botulinum toxin injections into affected muscles, according to standardized dosages [49], whereas paraneoplastic chorea can be treated with dopamine depletory agents (but caution should be used with these agents, to avoid tardive dyskinesia) [121]. Muscle relaxants such as benzodiazepines or Baclofen, along with Gabapentin, may help in the treatment of stiffness.

10. Conclusions

To summarize, with the present review we have provided an updated revision of the PMDs, including clinical features, associated antibodies, and underlying tumors commonly reported for each movement disorder. We strongly believe that clinicians should be aware of these rare but life-threatening conditions and be able to correctly diagnose and manage them. When dealing with a suspect PMD, clinicians should rapidly start a diagnostic-therapeutic work-up based on imaging and antibodies testing, promptly proposing immunotherapies when necessary.

Future perspectives imply a) broader diffusion of validated kits for the detection of the pathogenic antibodies, b) regional/national networks connecting unserved laboratories to the expertise of highly qualified centers, and c) enrollment of patients in clinical trials to test new possibly disease-modifying drugs. Ultimately, earlier detection of such conditions is crucial for the therapeutic success, drastically increasing the patient's chance of retaining the best quality of life possible. In conclusion, PMDs represent easily perceivable symptoms for the clinician during the patient evaluation. If we are aware of these rare disorders, the recognition will be beneficial both for the patient outcome and for our understanding of the molecular and immunological characteristics of this condition.

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References

[1] Dalmau J, Rosenfeld MR. Paraneoplastic syndromes of the CNS. Lancet Neurol 2008;7:327–40. https://doi.org/10.1016/S1474-4422(08)70060-7.
[2] Darnell RB, Posner J. Paraneoplastic syndromes involving the nervous system. N Engl J Med 2003;349(16):1543–54. https://doi.org/10.1056/NEJMra023009.
[3] Pittock SJ, Lucchinetti CF, Parisi JE, Benarroch EE, Mokri B, Stephan CL, et al. Amphiphysin autoimmunity: paraneoplastic accompaniments. Ann Neurol 2005;58:96–107. https://doi.org/10.1002/ana.20529.
[4] Viala K, Béhin A, Maisonobe T, Léger JM, Stojkovic T, Davi F, et al. Neuropathy in lymphoma: a relationship between the pattern of neuropathy, type of lymphoma and prognosis? J Neurol Neurosurg Psychiatry 2008;79(7):778–82. https://doi.org/10.1136/jnnp.2007.125930.
[5] Giometto B, Grisold W, Vitaliani R, Graus F, Honnorat J, Bertolini G. Paraneoplastic neurologic syndrome in the PNS euronetwork database: a European study from 20 centers. Arch Neurol 2010;67(3):330–5. https://doi.org/10.1001/archneurol.2009.341.
[6] Graus F, Delattre JY, Antoine JC, Dalmau J, Giometto B, Grisold W, et al. Recommended diagnostic criteria for paraneoplastic neurological syndromes. J Neurol Neurosurg Psychiatry 2004;75(8):1135–40. https://doi.org/10.1136/jnnp.2003.034447.
[7] Chan A, Baehring J. Paraneoplastic neurological syndromes: a single institution 10-year case series. J Neuro-Oncol 2019;141:431–9. https://doi.org/10.1007/s11060-018-03053-3.
[8] Baizabal-Carvallo JF, Jankovic J. Movement disorders in autoimmune diseases. Mov Disord 2012;27(8):935–46. https://doi.org/10.1002/mds.25011.
[9] Fahn S, Jankovic J, Hallett M. Principles and Practice of Movement Disorders. 2nd ed. 2011. https://doi.org/10.1016/C2009-0-44357-5.
[10] Albert ML, Austin LM, Darnell RB. Detection and treatment of activated T cells in the cerebrospinal fluid of patients with paraneoplastic cerebellar degeneration. Ann Neurol 2000;47(1):9–17. https://doi.org/10.1002/1531-8249(200001)47:1<9::AID-ANA5>3.0.CO;2-I.
[11] Dalmau J, Gleichman AJ, Hughes EG, Rossi JE, Peng X, Lai M, et al. Anti-NMDA-receptor encephalitis: case series and analysis of the effects of antibodies. Lancet Neurol 2008;7(12):1091–8. https://doi.org/10.1016/S1474-4422(08)70224-2.
[12] Fukuda T, Motomura M, Nakao Y, et al. Reduction of P/Q-type calcium channels in the postmortem cerebellum of paraneoplastic cerebellar degeneration with Lambert-Eaton myasthenic syndrome. Ann Neurol 2003;53:21–8. https://doi.org/10.1002/ana.10392.
[13] Honorat JA, Komorowski L, Josephs KA, Fechner K, Louis EKS, Hinson SR, et al. IgLON5 antibody - neurological accompaniments and outcomes in 20 patients. Neurol Neuroimmunol Neuroinflamm 2017;4(5):e385https://doi.org/10.1212/NXI.0000000000000385.
[14] Vernino S, Low PA, Fealey RD, Stewart JD, Farrugia G, Lennon VA. Autoantibodies to ganglionic acetylcholine receptors in autoimmune autonomic neuropathies. N Engl J Med 2000;343(847–55). https://doi.org/10.1056/NEJM200009213431204. 343(12):847–55.
[15] Edwards M, Stamelou M, Quinn N, Bhatia K. Parkinson's Disease and Other Movement Disorders. Oxford Univ Press; 2016.
[16] Armangue T, Sabater L, Torres-Vega E, Martinez-Hernandez E, Arino H, Petit-Pedrol M, et al. Clinical and immunological features of opsoclonus-myoclonus syndrome in the era of neuronal cell surface antibodies. JAMA Neurol 2016;73:417–24. https://doi.org/10.1001/jamaneurol.2015.4607.
[17] Bataller L, Graus F, Saiz A, Vilchez JJ. Clinical outcome in adult onset idiopathic or paraneoplastic opsoclonus-myoclonus. Brain 2001;124:437–43.
[18] Bataller L, Rosenfeld MR, Graus F, Vilchez JJ, Cheung N-K V, Dalmau J. Autoantigen diversity in the opsoclonus-myoclonus syndrome. Ann Neurol 2003;53:347–53. https://doi.org/10.1002/ana.10462.
[19] Arino H, Hoftberger R, Gresa-Arribas N, Martinez-Hernandez E, Armangue T, Kruer MC, et al. Paraneoplastic neurological syndromes and glutamic acid decarboxylase antibodies. JAMA Neurol 2015;72:874–81. https://doi.org/10.1001/jamaneurol.2015.0749.
[20] Blaes F, Dharmalingam B. Childhood opsoclonus-myoclonus syndrome: diagnosis and treatment. Expert Rev Neurother 2016;16:641–8. https://doi.org/10.1080/14737175.2016.1176914.
[21] Lamotte G, Danaila TC, Jaillon-Riviere V, Hitier M, Defer GL. Paraneoplastic opsoclonus myoclonus with autoantibodies to glutamic acid decarboxylase. Rev Neurol (Paris) 2014;170:50–1. https://doi.org/10.1016/j.neurol.2013.03.010.
[22] Lie G, Morley T, Chowdhury M. Paraneoplastic cerebellar degeneration as a marker of endometrial cancer recurrence. BMJ Case Rep 2016;2016. https://doi.org/10.1136/bcr-2016-215286.
[23] Matschke J, Kromminga A, Erbersdobler A, Lamszus K, Anders S, Köfüncü E. Paraneoplastic cerebellar degeneration and anti-Yo antibodies in a man with prostatic adenocarcinoma. J Neurol Neurosurg Psychiatry 2007;78(7):775–7. doi:https://doi.org/10.1136/jnnp.2006.112961.
[24] Meglič B, Graus F, Grad A. Anti-Yo-associated paraneoplastic cerebellar degeneration in a man with gastric adenocarcinoma. J Neurol Sci 2001;185(2):135–8. https://doi.org/10.1016/S0022-510X(01)00467-1.
[25] Rojas I, Graus F, Keime-Guibert F, Rene R, Delattre JY, Ramon JM, et al. Long-term clinical outcome of paraneoplastic cerebellar degeneration and anti-Yo antibodies. Neurology 2000;55:713–5.
[26] Debes J, Lagarde S, Hulsenboom E, et al. Anti-Yo-associated paraneoplastic cerebellar degeneration in a man with adenocarcinoma of the gastroesophageal junction. Dig Surg 2007;24:395–7. https://doi.org/10.1159/000107782.
[27] Bernal F, Shams'ili S, Rojas I, Sanchez-Valle R, Saiz A, Dalmau J, et al. Anti-Tr antibodies as markers of paraneoplastic cerebellar degeneration and Hodgkin's disease. Neurology 2003;60:230–4. https://doi.org/10.1212/01.WNL.0000041495.87539.98.
[28] Mason WP, Graus F, Lang B, Honnorat J, Delattre JY, Valldeoriola F, et al. Small-cell lung cancer, paraneoplastic cerebellar degeneration and the Lambert-Eaton myasthenic syndrome. Brain 1997;120(Pt 8):1279–300.
[29] Sabater L, Höftberger R, Boronat A, Saiz A. Antibody repertoire in paraneoplastic cerebellar degeneration and small cell lung cancer. PLoS One 2013;8:8–11. https://doi.org/10.1371/journal.pone.0060438.
[30] Graus F, Lang B, Pozo-Rosich P, Saiz A, Casamitjana R, Vincent A. P/Q type calcium-channel antibodies in paraneoplastic cerebellar degeneration with lung cancer. Neurology 2002;59:764–6. https://doi.org/10.1212/WNL.59.5.764.
[31] Yu Z, Kryzer TJ, Griesmann GE, Kim K, Benarroch EE, Lennon VA. CRMP-5 neuronal autoantibody: marker of lung cancer and thymoma-related autoimmunity. Ann Neurol 2001;49:146–54. https://doi.org/10.1002/1531-8249(20010201)49:2<146::AID-ANA34>3.0.CO;2-E.
[32] Chan KH, Vernino S, Lennon VA. ANNA-3 anti-neuronal nuclear antibody: marker of lung cancer-related autoimmunity. Ann Neurol 2001;50:301–11. https://doi.org/10.1002/ana.1127.
[33] Hasadsri L, Lee J, Wang BH, Yekkirala L, Wang M. Anti-yo associated paraneoplastic cerebellar degeneration in a man with large cell cancer of the lung. Case Rep Neurol Med 2013;2013:725936. https://doi.org/10.1155/2013/725936.
[34] Takasugi J, Shimamura M, Koda T, Kishikawa T, Hanamoto A, Inohara H, et al. Paraneoplastic cerebellar degeneration and Lambert-Eaton Myasthenic syndrome associated with neuroendocrine carcinoma of the oropharynx. Intern Med 2018;57:587–90. https://doi.org/10.2169/internalmedicine.9333-17.
[35] Dalmau J, Rosenfeld MR. Autoimmune encephalitis update. Neuro-Oncology 2014;16:771–8. https://doi.org/10.1093/neuonc/nou030.
[36] Titulaer MJ, McCracken L, Gabilondo I, Armangue T, Glaser C, Iizuka T, et al. Treatment and prognostic factors for long-term outcome in patients with anti-NMDA receptor encephalitis: an observational cohort study. Lancet Neurol 2013;12:157–65. https://doi.org/10.1016/S1474-4422(12)70310-1.
[37] Hoftberger R, van Sonderen A, Leypoldt F, Houghton D, Geschwind M, Gelfand J, et al. Encephalitis and AMPA receptor antibodies: novel findings in a case series of 22 patients. Neurology 2015;84:2403–12. https://doi.org/10.1212/WNL.0000000000001682.
[38] Irani SR, Pettingill P, Kleopa KA, Schiza N, Waters P, Mazia C, et al. Morvan syndrome: clinical and serological observations in 29 cases. Ann Neurol 2012;72:241–55. https://doi.org/10.1002/ana.23577.
[39] Graus F, Titulaer MJ, Balu R, Benseler S, Bien CG, Cellucci T, et al. A clinical approach to diagnosis of autoimmune encephalitis. Lancet Neurol 2016;15:391–404. https://doi.org/10.1016/S1474-4422(15)00401-9.
[40] Petit-Pedrol M, Armangue T, Peng X, Bataller L, Cellucci T, Davis R, et al. Encephalitis with refractory seizures, status epilepticus, and antibodies to the GABAA receptor: a case series, characterisation of the antigen, and analysis of the effects of antibodies. Lancet Neurol 2014;13:276–86. https://doi.org/10.1016/S1474-4422(13)70299-0.
[41] Mathew RM, Vandenberghe R, Garcia-Merino A, Yamamoto T, Landolfi JC, Rosenfeld MR, et al. Orchiectomy for suspected microscopic tumor in patients with anti-Ma2-associated encephalitis. Neurology 2007;68:900–5. https://doi.org/10.1212/01.wnl.0000252379.81933.80.
[42] Dalmau J, Graus F, Villarejo A, Posner JB, Blumenthal D, Thiessen B, et al. Clinical analysis of anti-Ma2-associated encephalitis. Brain 2004;127:1831–44. https://doi.org/10.1093/brain/awh203.
[43] Lancaster E, Lai M, Peng X, Hughes E, Constantinescu R, Raizer J, et al. Antibodies to the GABA(B) receptor in limbic encephalitis with seizures: case series and characterisation of the antigen. Lancet Neurol 2010;9:67–76. https://doi.org/10.1016/S1474-4422(09)70324-2.
[44] Moon J, Lee S-T, Shin J-W, Byun J-I, Lim J-A, Shin Y-W, et al. Non-stiff anti-amphiphysin syndrome: clinical manifestations and outcome after immunotherapy. J Neuroimmunol 2014;274:209–14. https://doi.org/10.1016/j.jneuroim.2014.07.011.
[45] Sahashi K, Sakai K, Mano K, Hirose G. Anti-Ma2 antibody related paraneoplastic limbic/brain stem encephalitis associated with breast cancer expressing Ma1, Ma2, and Ma3 mRNAs. J Neurol Neurosurg Psychiatry 2003;74:1332–5. https://doi.org/10.1136/jnnp.74.9.1332.
[46] Vigliani MC, Honnorat J, Antoine J-C, Vitaliani R, Giometto B, Psimaras D, et al. Chorea and related movement disorders of paraneoplastic origin: the PNS EuroNetwork experience. J Neurol 2011;258:2058–68. https://doi.org/10.1007/s00415-011-6074-1.
[47] O'Toole O, Lennon VA, Ahlskog JE, Matsumoto JY, Pittock SJ, Bower J, et al. Autoimmune chorea in adults. Neurology 2013;80:1133–44. https://doi.org/10.1212/WNL.0b013e3182886991.
[48] Vernino S, Tuite P, Adler CH, Meschia JF, Boeve BF, Boasberg P, et al. Paraneoplastic chorea associated with CRMP-5 neuronal antibody and lung carcinoma. Ann Neurol 2002;51:625–30. https://doi.org/10.1002/ana.10178.
[49] Balint B, Vincent A, Meinck HM, Irani SR, Bhatia KP. Movement disorders with neuronal antibodies: syndromic approach, genetic parallels and pathophysiology. Brain 2018;141(1):13–36. https://doi.org/10.1093/brain/awx189.
[50] Pittock SJ, Parisi JE, McKeon A, Roemer SF, Lucchinetti CF, Tan KM, et al. Paraneoplastic jaw dystonia and laryngospasm with antineuronal nuclear

autoantibody type 2 (anti-Ri). Arch Neurol 2010;67:1109–15. https://doi.org/10.1001/archneurol.2010.209.
[51] Pruss H, Voltz R, Flath B, Rudolph B, Klingebiel R, Zschenderlein R, et al. Anti-Ta-associated paraneoplastic encephalitis with occult testicular intratubular germ-cell neoplasia. J Neurol Neurosurg Psychiatry 2007;78:651–2. https://doi.org/10.1136/jnnp.2006.101964.
[52] Yap SM, Lynch T, MacMahon P, Murray B. Paraneoplastic atypical parkinsonism with anti CRMP 5 antibodies and severe caudate and putaminal hypometabolism on 18 fluorodeoxyglucose positron emission tomography of the brain. Mov Disord Clin Pract 2017;4:263–5. https://doi.org/10.1002/mdc3.12370.
[53] Hinson SR, Lopez-Chiriboga AS, Bower JH, Matsumoto JY, Hassan A, Basal E, et al. Glycine receptor modulating antibody predicting treatable stiff-person spectrum disorders. Neurol Neuroimmunol Neuroinflammation 2018;5:e438https://doi.org/10.1212/NXI.0000000000000438.
[54] Caviness JN, Forsyth PA, Layton DD, McPhee T. The movement disorder of adult opsoclonus. Mov Disord 1995;10:22–7. https://doi.org/10.1002/mds.870100106.
[55] Luque FA, Furneaux HM, Ferziger R, Rosenblum MK, Wray SH, Schold SC, et al. Anti-Ri: an antibody associated with paraneoplastic opsoclonus and breast cancer. Ann Neurol 1991;29(3):241–51. https://doi.org/10.1002/ana.410290303.
[56] Gallerini S, Marsili L, Marconi R. Opsoclonus-myoclonus syndrome in the era of neuronal cell surface antibodies: a message for clinicians. JAMA Neurol 2016;73(7):891. https://doi.org/10.1001/jamaneurol.2016.1161.
[57] Graus F, Ariño H, Dalmau J. Paraneoplastic neurological syndromes in Hodgkin and non-Hodgkin lymphomas. Blood 2014;123(21):3230–8. https://doi.org/10.1182/blood-2014-03-537506.
[58] Peterson K, Rosenblum MK, Kotanides H, Posner JB. Paraneoplastic cerebellar degeneration. I. a clinical analysis of 55 anti-Yo antibody-positive patients. Neurology 1992;42(10):1931–7. https://doi.org/10.1212/WNL.42.10.1931.
[59] Shams'Ili S, Grefkens J, De Leeuw B, Van den Bent M, Hooijkaas H, Van der Holt B, et al. Paraneoplastic cerebellar degeneration associated with antineuronal antibodies: analysis of 50 patients. Brain 2003;126(Pt 6):1409–18. https://doi.org/10.1093/brain/awg133.
[60] Storstein A, Raspotnig M, Vitaliani R, Giometto B, Graus F, Grisold W, et al. Prostate cancer, Hu antibodies and paraneoplastic neurological syndromes. J Neurol 2016;263(5):1001–7. https://doi.org/10.1007/s00415-016-8090-7.
[61] Verschnuren J, Chuang L, Rosenblum MK, Lieberman F, Pryor A, Posner JB, et al. Inflammatory infiltrates and complete absence of Purkinje cells in anti-Yo-associated paraneoplastic cerebellar degeneration. Acta Neuropathol 1996;91(5):519–25. https://doi.org/10.1007/s004010050460.
[62] Giometto B, Marchiori GC, Nicolao P, Scaravilli T, Lion A, Bardin PG, et al. Subacute cerebellar degeneration with anti-Yo autoantibodies: immunohistochemical analysis of the immune reaction in the central nervous system. Neuropathol Appl Neurobiol 1997;23(6):468–74. https://doi.org/10.1111/j.1365-2990.1997.tb01323.x.
[63] Rojas-Marcos I, Graus F, Sanz G, Robledo A, Diaz-Espejo C. Hypersomnia as presenting symptom of anti-Ma2-associated encephalitis: case study. Neuro-Oncology 2007;9(1):75–7. https://doi.org/10.1215/15228517-2006-013.
[64] Venkatraman A, Opal P. Paraneoplastic cerebellar degeneration with anti-Yo antibodies - a review. Ann Clin Transl Neurol 2016;3(8):655–63. https://doi.org/10.1002/acn3.328.
[65] Henke C, Rieger J, Hartmann S, Middendorp M, Steinmetz H, Ziemann U. Paraneoplastic cerebellar degeneration associated with lymphoepithelial carcinoma of the tonsil. BMC Neurol 2013;13:147. https://doi.org/10.1186/1471-2377-13-147.
[66] Lancaster E. The diagnosis and treatment of autoimmune encephalitis. J Clin Neurol 2016;12(1):1–13. https://doi.org/10.3988/jcn.2016.12.1.1.
[67] Leypoldt F, Wandinger K-P, Bien CG, Dalmau J. Autoimmune encephalitis. Eur Neurol Rev 2013;8. https://doi.org/10.17925/enr.2013.08.01.31. 31–7.
[68] Schein F, Gagneux-Brunon A, Antoine JC, Lavernhe S, Pillet S, Paul S, et al. Anti-N-methyl-d-aspartate receptor encephalitis after herpes simplex virus-associated encephalitis: an emerging disease with diagnosis and therapeutic challenges. Infection 2017;45(4):545–9. https://doi.org/10.1007/s15010-016-0959-y.
[69] van der Meulen AAE, van der Hoeven JH, de Jong BM, Elting JWJ. Extreme delta brushes in anti NMDA receptor encephalitis – muscle artefact or an EEG phenomenon? A case report. Clin. Neurophysiol. 2017;128(10):1835–6. https://doi.org/10.1016/j.clinph.2017.06.256.
[70] Varley JA, Webb AJS, Balint B, Fung VSC, Sethi KD, Tijssen MAJ, et al. The movement disorder associated with NMDAR antibody-encephalitis is complex and characteristic: an expert video-rating study. J Neurol Neurosurg Psychiatry 2018. https://doi.org/10.1136/jnnp-2018-318584.
[71] Lai M, Huijbers MGM, Lancaster E, Graus F, Bataller L, Balice-Gordon R, et al. Investigation of LGI1 as the antigen in limbic encephalitis previously attributed to potassium channels: a case series. Lancet Neurol 2010;9(8):776–85. https://doi.org/10.1016/S1474-4422(10)70137-X.
[72] Granerod J, Ambrose HE, Davies NWS, Clewley JP, Walsh AL, Morgan D, et al. Causes of encephalitis and differences in their clinical presentations in England: a multicentre, population-based prospective study. Lancet Infect Dis 2010;10(12):835–44. https://doi.org/10.1016/S1473-3099(10)70222-X.
[73] Andrade DM, Tai P, Dalmau J, Wennberg R. Tonic seizures: a diagnostic clue of anti-LGI1 encephalitis? Neurology 2011;76:1355–7. https://doi.org/10.1212/WNL.0b013e3182152808.
[74] Irani SR, Michell AW, Lang B, Pettingill P, Waters P, Johnson MR, et al. Faciobrachial dystonic seizures precede Lgi1 antibody limbic encephalitis. Ann Neurol 2011;69(5):892–900. https://doi.org/10.1002/ana.22307.
[75] Lancaster E, Huijbers MGM, Bar V, Boronat A, Wong A, Martinez-Hernandez E, et al. Investigations of caspr2, an autoantigen of encephalitis and neuromyotonia. Ann Neurol 2011;69(2):303–11. https://doi.org/10.1002/ana.22297.
[76] Boronat A, Sabater L, Saiz A, Dalmau J, Graus F. GABAB receptor antibodies in limbic encephalitis and anti-GAD-associated neurologic disorders. Neurology 2011;76(9):795–800. https://doi.org/10.1212/WNL.0b013e31820e7b8d.
[77] Rosenfeld MR, Eichen JG, Wade DF, Posner JB, Dalmau J. Molecular and clinical diversity in paraneoplastic immunity to Ma proteins. Ann Neurol 2001;50(3):339–48. https://doi.org/10.1002/ana.1288.abs.
[78] Matsumoto L, Yamamoto T, Higashihara M, Sugimoto I, Kowa H, Shibahara J, et al. Severe hypokinesis caused by paraneoplastic anti-Ma2 encephalitis associated with bilateral intratubular germ-cell neoplasm of the testes. Mov Disord 2007;22(5):728–31. https://doi.org/10.1002/mds.21314.
[79] Castle J, Sakonju A, Dalmau J, Newman-Toker DE. Anti-Ma2-associated encephalitis with normal FDG-PET: a case of pseudo-Whipple's disease. Nat Clin Pract Neurol 2006;2(10):566–72. https://doi.org/10.1038/ncpneuro0287.
[80] Hoffmann LA, Jarius S, Pellkofer HL, Schueller M, Krumbholz M, Koenig F, et al. Anti-Ma and anti-Ta associated paraneoplastic neurological syndromes: 22 newly diagnosed patients and review of previous cases. J Neurol Neurosurg Psychiatry 2008;79(7):767–73. https://doi.org/10.1136/jnnp.2007.118588.
[81] Attarian H, Applebee G, Von Lepel A. Paraneoplastic myoclonus with papillary thyroid carcinoma. Eur Neurol 2007;58(3):182–3. https://doi.org/10.1159/000104721.
[82] Klaas JP, Ahlskog JE, Pittock SJ, Matsumoto JY, Aksamit AJ, Bartleson JD, et al. Adult-onset opsoclonus-myoclonus syndrome. Arch Neurol 2012;69(12):1598–607. https://doi.org/10.1001/archneurol.2012.1173.
[83] Honorat JA, McKeon A. Autoimmune movement disorders: a clinical and laboratory approach. Curr Neurol Neurosci Rep 2017;17(1):4. https://doi.org/10.1007/s11910-017-0709-2.
[84] Gresa-Arribas N, Planagumà J, Petit-Pedrol M, Kawachi I, Katada S, Glaser CA, et al. Human neurexin-3α antibodies associate with encephalitis and alter synapse development. Neurology 2016. https://doi.org/10.1212/WNL.0000000000002775.
[85] Mohammad SS, Fung VSC, Grattan-Smith P, Gill D, Pillai S, Ramanathan S, et al. Movement disorders in children with anti-NMDAR encephalitis and other autoimmune encephalopathies. Mov Disord 2014;86(24):2235–42. https://doi.org/10.1002/mds.25999.
[86] Mohammad SS, Wallace G, Ramanathan S, Brilot F, Dale RC. Antipsychotic-induced isia and neuroleptic malignant syndrome in anti-NMDAR encephalitis. Ann Clin Psychiatry 2014;26(4):297–8.
[87] Vincent A, Buckley C, Lang B, Irani S. Clinical spectrum of voltage-gated potassium channel autoimmunity. Neurology 2009;72(1):99. https://doi.org/10.1212/01.wnl.0000339405.94708.8.
[88] Tobin WO, Lennon VA, Komorowski L, Probst C, Clardy SL, Aksamit AJ, et al. DPPX potassium channel antibody: frequency, clinical accompaniments, and outcomes in 20 patients. Neurology 2014;83(20):1797–803. https://doi.org/10.1212/WNL.0000000000000991.
[89] Grant R, Graus F. Paraneoplastic movement disorders. Mov Disord 2009;24:1715–24. https://doi.org/10.1002/mds.22658.
[90] Colosimo C, Bak TH, Bologna M, Berardelli A. Fifty years of progressive supranuclear palsy. J Neurol Neurosurg Psychiatry 2014;85(8):938–44. https://doi.org/10.1136/jnnp-2013-305740.
[91] Panzer J, Dalmau J. Movement disorders in paraneoplastic and autoimmune disease. Curr Opin Neurol 2011;24(4):346–53. https://doi.org/10.1097/WCO.0b013e328347b307.
[92] Tan JH, Goh BC, Tambyah PA, Wilder-Smith E. Paraneoplastic progressive supranuclear palsy syndrome in a patient with B-cell lymphoma. Parkinsonism Relat Disord 2005;11(3):187–91. https://doi.org/10.1016/j.parkreldis.2004.09.003.
[93] Fahn S, Brin MF, Dwork AJ, Weiner WJ, Goetz CG, Rajput AH. What is it? Case 1, 1996: rapidly progressive parkinsonism, incontinence, impotency, and levodopa-induced moaning in a patient with multiple myeloma. Mov Disord 1996;11(3):298–310. https://doi.org/10.1002/mds.870110314.
[94] Meinck HM, Thompson PD. Stiff man syndrome and related conditions. Mov Disord 2002;17(5):853–66. https://doi.org/10.1002/mds.10279.
[95] Ishii A, Hayashi A, Ohkoshi N, Matsuno S, Shoji S. Progressive encephalomyelitis with rigidity associated with anti-amphiphysin antibodies. J Neurol Neurosurg Psychiatry 2004;75(4):661–2. https://doi.org/10.1136/JNNP.2003.010504.
[96] Carvajal-González A, Leite MI, Waters P, Woodhall M, Coutinho E, Balint B, et al. Glycine receptor antibodies in PERM and related syndromes: characteristics, clinical features and outcomes. Brain 2014;137(Pt 8):2178–92. https://doi.org/10.1093/brain/awu142.
[97] Klein CJ, Lennon VA, Aston PA, McKeon A, Pittock SJ. Chronic pain as a manifestation of potassium channel-complex autoimmunity. Neurology 2012;79(11):1136–44. https://doi.org/10.1212/WNL.0b013e3182698cab.
[98] Vincent A, Pettingill P, Pettingill R, Lang B, Birch R, Waters P, et al. Association of Leucine-Rich Glioma inactivated protein 1, contactin-associated protein 2, and contactin 2 antibodies with clinical features and patient-reported pain in acquired neuromyotonia. JAMA Neurol 2018;75:1519–27. https://doi.org/10.1001/jamaneurol.2018.2681.
[99] Linke R, Schroeder M, Helmberger T, Voltz R. Antibody-positive paraneoplastic neurologic syndromes: value of CT and PET for tumor diagnosis. Neurology 2004;63(2):282–6. https://doi.org/10.1212/01.WNL.0000129983.06983.4E.
[100] Titulaer MJ, Soffietti R, Dalmau J, Gilhus NE, Giometto B, Graus F, et al. Screening for tumours in paraneoplastic syndromes: report of an EFNS task force. Eur J Neurol 2011;18(1):19–3. https://doi.org/10.1111/j.1468-1331.2010.03220.x.
[101] Younes-Mhenni S, Janier MF, Cinotti L, Antoine JC, Tronc F, Cottin V, et al. FDG-PET improves tumour detection in patients with paraneoplastic neurological syndromes. Brain 2004;127(Pt 10):2331–8. https://doi.org/10.1093/brain/

awh247.
[102] Zoccarato M, Gastaldi M, Zuliani L, Biagioli T, Brogi M, Bernardi G, et al. Diagnostics of paraneoplastic neurological syndromes. Neurol Sci 2017;38(Suppl. 2):237–42. https://doi.org/10.1007/s10072-017-3031-5.
[103] Gresa-Arribas N, Titulaer MJ, Torrents A, Aguilar E, McCracken L, Leypoldt F, et al. Antibody titres at diagnosis and during follow-up of anti-NMDA receptor encephalitis: a retrospective study. Lancet Neurol 2014;13(2):167–77. https://doi.org/10.1016/S1474-4422(13)70282-5.
[104] Cervera R, Piette JC, Font J, Khamashta MA, Shoenfeld Y, Camps MT, et al. Antiphospholipid syndrome: clinical and immunologic manifestations and patterns of disease expression in a cohort of 1,000 patients. Arthritis Rheum 2002;46(4):1019–27. https://doi.org/10.1002/art.10187.
[105] Yelnik CM, Kozora E, Appenzeller S. Non-stroke central neurologic manifestations in antiphospholipid syndrome. Curr Rheumatol Rep 2016;18(2):11. https://doi.org/10.1007/s11926-016-0568-x.
[106] Fleetwood T, Cantello R, Comi C. Antiphospholipid syndrome and the neurologist: from pathogenesis to therapy. Front Neurol 2018;9:1001. https://doi.org/10.3389/fneur.2018.01001.
[107] Dale RC, Merheb V, Pillai S, Wang D, Cantrill L, Murphy TK, et al. Antibodies to surface dopamine-2 receptor in autoimmune movement and psychiatric disorders. Brain 2012;135(Pt 11):3453–68. https://doi.org/10.1093/brain/aws256.
[108] Laurent C, Capron J, Quillerou B, Thomas G, Alamowitch S, Fain O, et al. Steroid-responsive encephalopathy associated with autoimmune thyroiditis (SREAT): characteristics, treatment and outcome in 251 cases from the literature. Autoimmun Rev 2016;15(12):1129–33. https://doi.org/10.1016/j.autrev.2016.09.008.
[109] Álvarez Bravo G, Yusta Izquierdo A, Carvalho Monteiro G, Sánchez I. Cerebellopathy secondary to anti-peroxidase antibody-mediated toxicity. A special case of Hashimoto encephalopathy. J Neuroimmunol 2017;312:1–3. https://doi.org/10.1016/j.jneuroim.2017.08.007.
[110] Spatola M, Petit-Pedrol M, Simabukuro MM, Armangue T, Castro FJ, Artigues MIB, et al. Investigations in GABAA receptor antibody-associated encephalitis. Neurology 2017;88(11):1012–20. https://doi.org/10.1212/WNL.0000000000003713.
[111] Hacohen Y, Wright S, Waters P, Agrawal S, Carr L, Cross H, et al. Paediatric autoimmune encephalopathies: clinical features, laboratory investigations and outcomes in patients with or without antibodies to known central nervous system autoantigens. J Neurol Neurosurg Psychiatry 2013;84(7):748–55. https://doi.org/10.1136/jnnp-2012-303807.
[112] Kirvan CA, Swedo SE, Heuser JS, Cunningham MW. Mimicry and autoantibody-mediated neuronal cell signaling in Sydenham chorea. Nat Med 2003;9(7):914–20. https://doi.org/10.1038/nm892.
[113] Dale RC, Candler PM, Church AJ, Wait R, Pocock JM, Giovannoni G. Neuronal surface glycolytic enzymes are autoantigen targets in post-streptococcal autoimmune CNS disease. J Neuroimmunol 2006;172(1–2):187–97. https://doi.org/10.1016/j.jneuroim.2005.10.014.
[114] Ben-Pazi H, Stoner JA, Cunningham MW. Dopamine receptor autoantibodies correlate with symptoms in Sydenham's chorea. PLoS One 2013;8(9):e73516https://doi.org/10.1371/journal.pone.0073516.
[115] Gaig C, Graus F, Compta Y, Högl B, Bataller L, Brüggemann N, et al. Clinical manifestations of the anti-IgLON5 disease. Neurology 2017;88(18):1736–43. https://doi.org/10.1212/WNL.0000000000003887.
[116] Sabater L, Gaig C, Gelpi E, Bataller L, Lewerenz J, Torres-Vega E, et al. A novel non-rapid-eye movement and rapid-eye-movement parasomnia with sleep breathing disorder associated with antibodies to IgLON5: a case series, characterisation of the antigen, and post-mortem study. Lancet Neurol 2014;13(6):575–86. https://doi.org/10.1016/S1474-4422(14)70051-1.
[117] Hatano T, Shimada Y, Kono A, Kubo SI, Yokoyama K, Yoritaka A, et al. Atypical miller fisher syndrome associated with glutamate receptor antibodies. BMJ Case Rep 2011. https://doi.org/10.1136/bcr.08.2010.3228.
[118] Zuliani L, Sabater L, Saiz A, Baiges JJ, Giometto B, Graus F. Homer 3 autoimmunity in subacute idiopathic cerebellar ataxia. Neurology 2007;68(3):239–40. https://doi.org/10.1212/01.wnl.0000251308.79366.f9.
[119] Höftberger R, Sabater L, Ortega A, Dalmau J, Graus F. Patient with Homer-3 antibodies and cerebellitis. JAMA Neurol 2013;70(4):506–9. https://doi.org/10.1001/jamaneurol.2013.1955.
[120] Darnell RB, Furneaux HM, Posner JB. Antiserum from a patient with cerebellar degeneration identifies a novel protein in Purkinje cells, cortical neurons, and neuroectodermal tumors. J Neurosci 1991;11(5):1224–30. https://doi.org/10.1523/JNEUROSCI.11-05-01224.
[121] Cardoso F. Autoimmune choreas. J Neurol Neurosurg Psychiatry 2017;88:412–7. https://doi.org/10.1136/jnnp-2016-314475.
[122] Gilhus N. Neuromuscular junction disorders. In: Colosimo C, Gil-Nagel A, Gilhus NE, Rapoport A, Williams O, editors. Handb Neurol Ther. 2015. p. 177–85.