Karolina Popławska-Domaszewicz*, Jolanta Florczak-Wyspiańska, Wojciech Kozubski and Sławomir Michalak

Paraneoplastic movement disorders

https://doi.org/10.1515/revneuro-2017-0081
Received October 15, 2017; accepted January 26, 2018

Abstract: Paraneoplastic movement disorders are rare, autoimmune-mediated, nonmetastatic complications of malignant neoplasms. Common paraneoplastic movement disorders include paraneoplastic chorea, dystonia, cerebellar degeneration, different types of encephalitis, opsoclonus-myoclonus syndrome, stiff person syndrome, and neuromyotonia. Syndromes usually develop before tumor diagnosis, have subacute onset, and are associated with serum or cerebrospinal fluid antibodies. Two types of antibodies can be distinguished: antibodies against nuclear and cytoplasmic neuronal antigens (anti-Hu, anti-Ri, anti-Yo, anti-Ma, anti-CV2/CRMP5, anti-Gephrin, and anti-GABATRAP) and antibodies recently identified against cell surface and synaptic proteins (anti-NMDAR, anti-LGI1, and anti-Caspr2). These two types differ from each other in a few important aspects. Antibodies against cell surface and synaptic protein disrupt cell-surface antigens. Clinical symptoms are related to the disruption of antigens and potentially can be reversed by immunotherapy. The association between these antibodies and malignancy is much less consistent. On the other hand, antibodies against nuclear and cytoplasmic neuronal antigens seem to be not pathogenic; however, they most likely indicate a T-cell-mediated immune response against neurons. Due to T-cell-mediated neuronal loss, response to immunotherapy is generally disappointing. Early recognition of all these diseases is crucial because it may lead to the disclosure of occult cancer. This review is focused on paraneoplastic movement disorders with emphasis on clinical presentations, investigational findings, and therapeutic results.

***Corresponding author: Karolina Popławska-Domaszewicz,** Department of Neurology, Poznan University of Medical Sciences, 49, Przybyszewskiego Str., 60355 Poznan, Poland, e-mail: poplawska.domaszewicz@gmail.com
Jolanta Florczak-Wyspiańska and Wojciech Kozubski: Department of Neurology, Poznan University of Medical Sciences, 49, Przybyszewskiego Str., 60355 Poznan, Poland
Sławomir Michalak: Department of Neurochemistry and Neuropathology, Poznan University of Medical Sciences, 49, Przybyszewskiego Str., 60355 Poznan, Poland

Keywords: immunotherapy; onconeuronal antibodies; paraneoplastic movement disorders.

Introduction

Paraneoplastic neurological syndromes (PNS) are – in general – rare conditions and occur as a remote effect of malignant tumors, mostly cancers, not directly caused by local mass invasion, metastases, infections, nutritional factors, or anti-tumor treatment (Posner and Davines, 1995). A subacute clinical course along with inflammatory changes in the cerebrospinal fluid (CSF) may suggest the diagnosis of PNS (Psimaras et al., 2010); however, a more specific finding is the presence of onconeuronal antibodies. The classical/well-defined onconeuronal antibodies, such as Hu, Yo, and Ma2, are created against intracellular antigens and are strongly associated with underlying tumors (Stich et al., 2007). The pathogenic role of these antibodies remains unclear. Multiple studies in animals to reproduce PNS by passive transfer experiments or active vaccination have failed; therefore, they seem to be not directly pathogenic (Sillevis Smitt et al., 1995; Tanaka et al., 1995). However, they indicate a T-cell-mediated immune response against neurons (Darnell and Posner, 2003). Possible exceptions are amphiphysin and Yo antibodies, which might be pathogenic (Sommer et al., 2005; Geis et al., 2009, 2010; Greenlee et al., 2015). Geis et al. (2012) reported that intrathecal application of purified immunoglobulin G-antibodies against amphiphysin from a patient with paraneoplastic stiff person syndrome (SPS) with high titer of anti-amphiphysin antibodies induces anxiety behavior in rats. It can be explained by binding of anti-amphiphysin antibodies to brain structures which are associated with anxiety disorders, such as the hippocampus-amygdala region (Geis et al., 2012). Moreover, it has been hypothesized that anti-amphiphysin antibodies disturbed vesicular endocytosis preferentially in GABAergic synapses leading to a reduction in transmitter release and diminished GABAergic inhibition in spinal cord circuitries (Geis et al., 2010). It has been postulated that also anti-Yo antibodies can be pathogenic. Greenlee et al. (2015) demonstrated that anti-Yo antibodies, by binding to the intracellular 62 kDa Yo antigen, cause Purkinje cell death. Due to T-cell-mediated cell death and neuronal loss, response

to immunotherapy is generally disappointing (Table 1). Stabilizing the neurological course is the main therapeutic purpose. Recent studies have identified antibodies against cell surface or synaptic proteins associated with encephalitis. The antigens associated to this group are *N*-methyl-D-aspartate receptor (NMDAR) (Dalmau et al., 2007), the α-amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid receptor (AMPAR) (Lai et al., 2009), the γ-aminobutyric acid receptor-B ($GABA_B$ receptor) (Lancaster et al., 2010), leucine-rich glioma-inactivated protein 1 (LGI1), and contactin-associated protein-like 2 (Caspr2) (previously thought to be voltage-gated potassium channels) (Irani et al., 2010a,b; Lai et al., 2010; Lancaster et al., 2011), the glycine receptor (GlyR) (Hutchinson et al., 2008), and the metabotropic glutamate receptor mGluR5 (Lancaster et al., 2011). These antibodies differ from those targeting on intracellular antigens in a few important aspects. First, they disrupt cell-surface antigens, and symptoms are related to the disruption of antigens and are similar to a pharmacological blockade of the recognized antigen. The association with malignancy is much less consistent. Neurological deficits can be potentially reversed by immunotherapy (Lancaster and Dalmau, 2012). Early identification of PNS is important, because it may lead to the diagnosis of occult cancer. In 2011 European Federation of Neurological Societies Task Force published screening recommendation for classical PNS (Titulaer et al., 2011). This review focused on paraneoplastic movement disorders (PMD) with emphasis on clinical presentations, investigational findings, and therapeutic results.

Paraneoplastic chorea

Paraneoplastic chorea typically affects adults over 60 years with subacute onset (O'Toole et al., 2013). Chorea may be focal or generalized (O'Toole et al., 2013). Most patients present classic choreoathetosis with symmetric involvement of the trunk and neck; however, symptoms may be unilateral (Vigliani et al., 2011). Chorea often coexists with other neurological syndromes – the most frequent is peripheral neuropathy (O'Toole et al., 2013) – but encephalitis, psychiatric disturbances, or visual deficits also might be present (Vigliani et al., 2011). The disorder usually associates with CRMP5 and Hu antibodies. Small cell lung cancer (SCLC) and various adenocarcinomas are the most frequent associated tumors (O'Toole et al., 2013). Moreover, lymphoma or bowel or kidney cancers are also reported. Detection of specific antibodies is crucial to confirm the PNS; however, their absence does not exclude the diagnosis. CSF analysis can be normal or present non-specific inflammatory changes. Brain magnetic resonance imaging (MRI) studies are usually normal. When abnormal, they reveal hyperintensities involving basal ganglia, which may be transient, or diffuse leukoencephalopathy (Vigliani et al., 2011). The survival outcome depends usually on the oncological disease but is generally poor, ranging from 6 months to 1 year and a half (O'Toole et al., 2013). Honnorat and colleagues reported that median survival is longer in patients with SCLC and anti-CRMP5-related encephalitis than those with anti-Hu-related encephalitis (Honnorat et al., 2009).

Stiff person syndrome

Stiff person syndrome is a rare neurological disorder characterized by stiffness, progressive axial and proximal limb rigidity, and painful muscle cramps triggered by sensory or emotional stimuli (Lorish et al., 1989; Thompson, 1994; Spay and Chen, 2006). Symptoms often restrict voluntary movements: patients have difficulty with bending over, walking, and rotation of the head to look to the side or back. Thereby they adopt a typical hyperlordotic lumbar posture, which persists even when lying down on their back. Symptoms typically start slowly, fluctuate in intensity from hour to hour or from day to day, usually disappearing during sleep; symptoms are usually symmetrical (Lorish et al., 1989). Psychiatric features including fear, anxiety, and phobias are frequent and can give impression of psychogenic disorder that delays the diagnosis. These symptoms can result with the falls or dysregulation in the structures of the brain such as the amygdala and hippocampus (Rakocevic et al., 2004; Ameli et al., 2005).

Electromyography (EMG) studies typically reveal continuous motor unit activity more prominent in paraspinal muscles (thoracolumbar and rectus abdominis) and proximal limb muscles. Usually, simultaneous involvement of the agonist and antagonist muscle groups is present (Brown and Marsden, 1999). Disease can be manifested as idiopathic or paraneoplastic (Dalakas et al., 2000). Barker and coworkers divided SPS into three distinct categories: SPS, progressive encephalomyelitis with rigidity, and stiff-limb syndrome – a focal form of the disorder (Barker et al., 1998). Brown and Marsden (1999) proposed the new classification – separating the classic form (SPS) from a distinct group designated as 'stiff-man plus' syndrome that includes both the clinically atypical presentations and the paraneoplastic forms of the disease. The paraneoplastic SPS presents as stiffness mostly in the neck and arms, spinal myoclonus, and pruritis. In contrast with patients with typical form, distribution of

Table 1: Treatment of PNS with onconeuronal antibodies.

Study	Type of study	Antibodies	Numbers of patients	Treatment	Outcomes
Dalmau et al. (2004)	Retrospective	Ma2	38	Tumor therapy, immunotherapy	30% with favorable outcome 20% stabilization of neurological state 50% with clinical degradation
Uchuya et al. (1996)	Retrospective	Hu, Yo	21	IVIG	Improvement or stabilization in cases of subacute sensory neuropathy No improvement in central nervous system PNS
Keime-Guibert et al. (2000)	Retrospective	Hu, Yo, CV2	16	IVIG, corticoids, cyclophosphamide	Mostly stabilization of neurological symptoms
Shams'ili et al. (2003)	Retrospective	Hu, Yo, Ri, DNER	48	Tumor treatment, immunosuppression	Few patients improved after tumor therapy
Sillevis Smitt et al. (2002)	Retrospective	Hu	73	PE, corticoids, IVIG, cyclophosphamide, azathioprine	53% with improvement after tumor therapy 14% with improvement after only immunotherapy 25% with improvement after both methods of treatment 27% with no clinical improvement
Graus et al. (2001)	Retrospective	Hu	200	IVIG, corticoids, cyclophosphamide, PE	Infrequent clinical Improvement
Rojas et al. (2000)	Retrospective	Yo	19	Immunomodulation (not specified)	No improvement
Shams'ili et al. (2006)	Retrospective	Hu, Yo	9	Rituximab	4/9 with clinical improvement
Orange et al. (2012)	Retrospective	Hu, Yo, CV2	26	Tacrolimus	Few clinical improvement
Vernino and Lennon (2004)	Prospective	Hu, Yo, CV2	20	PE and cyclophosphamide vs PE and chemotherapy	Better outcome in patients treated with cyclophosphamide
van Broekhoven et al. (2010)	Prospective	Hu	15	hCG	A third of patients showed a significant improvement

hCG, human chorionic gonadotropin; ivIg, intravenous immunoglobulin; PE, plasma exchanges.

symptoms is distal and asymmetric (Pittock et al., 2005; Murinson and Guarnaccia, 2008). Paraneoplastic SPS is usually associated with antibodies against amphiphysin and SCLC and breast cancer (Antoine et al., 1999; Dorresteijn et al., 2002; Ishii et al., 2004). Moreover, antigephyrin antibodies have been described in patients with mediastinal malignant tumors (Butler et al., 2000). Antibodies against the α1 subunit of the glycine receptor have been reported in some patients with progressive encephalomyelitis with rigidity and myoclonus (PERM) (Hutchinson et al., 2008; Mas et al., 2011). These antibodies are associated with SCLC and chronic lymphocytic leukemia (Derksen et al., 2013; Kyskan et al., 2013). About 80% of patients with the most frequent idiopathic form of SPS have antibodies against glutamic acid decarboxylase 65 (GAD65) (Meinck and Thompson, 2002). GAD65 antibodies (GAD65-Ab) can also occur in patients with cerebellar ataxia, epilepsy, PNS, idiopathic limbic encephalitis, myasthenia gravis, and isolated type I diabetes mellitus. It is noteworthy that intrathecal synthesis of GAD65-ab is related to the neurological syndrome particularly when there is a concomitant DM1 that justifies the presence of high GAD65-ab levels (Saiz et al., 2008). It has been hypothesized that autoantibodies are a strict cause of SPS and cerebellar ataxia in individuals with GAD65-ab. However, it remains unclear whether the GAD65-ab themselves or other antibodies present in the patient's sera are pathogenic (Manto et al., 2007). Raju et al. reported that 70% of patients with SPS and GAD65-ab also have GABAA-receptor-associated protein (GABARAP) antibodies, which raises a question of which antibodies are pathogenic (Raju et al., 2006). The most frequent in paranoplastic form – anti-amphiphisin antibodies – mediate reduced GABAergic inhibition (Geis et al., 2010). The management of SPS includes corticosteroids, IVIg, and plasmapferesis (Brashear and Phillips, 1991; Gordon et al., 1991; Nakamagoe et al., 1995; Dalakas et al., 2001; Meinck 2001; De la Casa-Fages et al., 2013). Nakane and coworkers reported that tacrolimus at low doses is safe and effective in the long-term treatment and should be considered as an alternative use for patients with disabling SPS who are not responsive to conventional treatment (Nakane et al., 2013). Botulin toxin A improves symptoms in stiff limb syndrome (Anagnostou and Zambelis, 2012).

For paraneoplastic PERM with antiglycine receptor antibodies a benefit of rituximab has been demonstrated (Kyskan et al., 2013). Benzodiazepins, GABA-enhancing drugs, and pregabalin are usually beneficial in the symptomatic treatment (Vasconcelos and Dalakas, 2003; Squintani et al., 2012).

Opsoclonus-myoclonus ataxia syndrome

Opsoclonus-myoclonus ataxia syndrome (OMAS), traditionally described as 'dancing eyes, dancing feet syndrome', is a rare autoimmune condition that presents clinically with opsoclonus, myoclonus, and ataxia. Opsoclonus is characterized by bizarre, involuntary horizontal and vertical eye movements that are rapid, arrhythmic, and chaotic. Myoclonus is identified by sudden, quick jerks of a muscle or muscle group. Cerebellar signs include ataxia, dyspraxia, dysarthria, and dysphagia, along with hypotonia, lethargy, and malaise (Mitchell and Snodgrass, 1990). Etiology can be postinfectious, idiopathic, or paraneoplastic (Pranzatelli, 1996). Approximately half of the children with OMAS have neuroblastoma (Gorman, 2010). In adults, 50% of OMAS are idiopathic or infectious (Caviness et al., 1995). Paraneoplastic form accounts for about 20% of cases and is usually associated with lung, breast, and ovarian cancers, but other tumors like renal cell carcinoma and gastric adenocarcinoma may occur (Luque et al., 1991; Vigliani et al., 2011). Moreover, OMAS has been occasionally associated with a variety of tumors: thyroid, melanoma, pancreas, thymic carcinoma, gall bladder, neurofibrosarcoma, chondrosarcoma, and Hodgkin's disease (Bataller et al., 2001). Pathophysiology is not entirely clear. Symptoms of OMAS are caused by damage of the inhibitory Purkinje cells and granular neurons in the dorsal vermis of the cerebellum; however, some cases remain negative for autoantibodies and exhibit normal IgG concentrations (Blaes et al., 2005; Baets et al., 2006; Beck et al., 2007; Wong, 2007). Currently, there are no immunological markers to identify the adult patients with paraneoplastic OMAS. The specific anti-neuronal antibodies are not consistently found in OMAS patients (Bataller et al., 2001). Anti-Ri (most frequent), anti-Hu, anti-amphiphysin, anti-Yo, and anti-CV2/CRMP antibodies have been described in adult patients (Luque et al., 1991; Honnorat et al., 1997; Bataller et al., 2001; Gozzard and Maddison, 2010; Klaas et al., 2012). Neuroimaging examination (MRI, CT) is usually normal. Sometimes brain MRI shows an area of T2-increased signal in the thalamus. CSF examination can be normal but usually reveals mild increases in proteins and a lymphocytic pleocytosis consistent with inflammatory changes (Bataller et al., 2001; Scarff et al., 2011). The management of pediatric OMAS is directed at the etiology and involves resection of the neuroblastoma, if present, and immunotherapy, including corticosteroids, adrenocorticotropic hormone, IVIg, plasmapheresis, rituximab,

ofatumumab, or cyclophosphamide (Armstrong et al., 2005; Wilken et al., 2008; De Grandis et al., 2009; Pranzatelli et al., 2010, 2012). Despite positive initial response to immunomodulating therapy, multiple relapses are frequent (Mitchell et al., 2005; Brunklaus et al., 2011). Chronicity with lasting neurologic impairment (motor, speech, learning, and behavior problems) is primarily determined by severe initial symptoms and the very young age at disease onset (Brunklaus et al., 2011). In adults the prognosis is more favorable in OMAS of idiopathic origin. Corticosteroids or IVIg can accelerate recovery; however, residual gait ataxia tends to persist in older patients. By contrast, paraneoplastic form has a more severe clinical course and may be a life-threatening condition, particularly if underlying tumor is not diagnosed and treated. Only when malignancy is controlled can patient benefit from immunomodulatory treatment (Bataller et al., 2001).

Jaw dystonia and laryngospasm

Paraneoplastic neurologic dysfunction associated with anti-Ri antibody is multifocal but mainly affects the brainstem, cerebellum, and spinal cord. Jaw dystonia and laryngospasm are common accompaniments of Ri autoimmunity and can be reason of severe morbidity and mortality if unrecognized. Recently, Pittock and colleagues described nine patients who experienced intense jaw spasms and laryngospasm. Jaw dystonia interfered with mouth opening leading to nutritional complications. Laryngospasm was episodic, recurrent, and associated with respiratory distress. These patients also presented other symptoms suggestive of brainstem involvement. The most frequent associated tumor was breast cancer. Immunosuppressants, cytothoxic therapies, and botulinum toxicum were effective in some cases (Pittock et al., 2010) (see Table 2).

Extrapyramidal symptoms in paraneoplastic encephalitis

Anti-*N*-methyl-D-aspartate receptor encephalitis

Prominent features of anti-NMDAR encephalitis include psychiatric symptoms and signs like anxiety, insomnia, fear, delusions, hyper-religiosity, mania, and paranoia. Memory deficits, seizures, and language disintegration are also frequent. Usually the initial phase of illness progresses into a state of responsiveness with catatonic symptoms, abnormal movement, dysautonomia, and breathing difficulties (hypoventilation) (Dalmau et al., 2011). The most characteristic movements are oro-lingual-facial dyskinesias, but other types like ballismus, limb and trunk choreoathetosis with oculogyric deviation, opisthotonus, and dystonic limb posturing may occur. Moreover, parkinsonian syndrome, rigidity, and myoclonus may be present (Kleinig et al., 2008; Irani et al., 2010a,b; Dalmau et al., 2011). The coexistence of the dyskinetic movement with motor seizures can cause under-recognition of the seizures or an unnecessary escalation of antiepiletics for nonepileptic movements (Bayreuther et al., 2009).

Anti-NMDAR encephalitis is associated with ovarian teratoma and exceptionally with other neoplasms. However, men, children, and patients without tumor also can be affected (Dalmau et al., 2008; Irani et al., 2010a,b). Brain MRI can be normal or show T2/FLAIR hyperintensities of the hippocampus, cerebellum, cerebral cortex, subcortical regions, basal ganglia, or brainstem. CSF examination usually reveals inflammatory changes – lymphocytic pleocytosis and increased protein concentration (Dalmau et al., 2007). Recently, a novel EEG pattern named 'extreme delta brush' was identified in patients with anti-NMDAR encephalitis. The presence of this finding is associated with prolonged hospitalization but does not predict a worse outcome (de Graaff et al., 2012). Reversibility of this disorder is largely accepted. Iizuka et al. confirmed that brain atrophy that occurs in some patients is potentially reversible (Iizuka et al., 2010). It has been reported that about 75% of patients with NMDAR encephalitis have a favorable outcome with tumor resection and immunotherapy, i.e. corticosteroids, intravenous immunoglobulins, or plasma exchange. In some cases (delayed diagnosis or status without cancer) second line treatment (rituximab, cyclophosphamide, or both) is advised (Dalmau et al., 2011).

Anti-Ma2-associated encephalitis

Paraneoplastic anti-Ma2-associated encephalitis usually presents as limbic, diencephalic, and brainstem dysfunction (Rosenfeld et al., 2001; Dalmau et al., 2004). Short-term memory loss, seizures, confusion, hallucinations, mood disorder, or personality change are characteristic to this condition. Clinical symptoms of diencephalic encephalitis include excessive daytime sleepiness, narcolepsy-cataplexy, decrease of CSF hypocretin, hyperthermia, hypothalamic-pituitary endocrine dysfunction,

Table 2: Paraneoplastic movement disorders – characteristic features, associated antibodies and tumors, diagnostic procedures, and treatment.

Movement disorder	Symptoms	Antibodies	Tumor	Diagnostic	Treatment
Chorea (O'Toole et al., 2013)	Choreoathetosis with involvement of the trunk and neck (symmetric or unilateral) (Vigliani et al., 2011) Peripheral neuropathy (O'Toole et al., 2013) Encephalitis, psychiatric disturbances, visual deficits (Vigliani et al., 2011)	CRMP5, Hu (O'Toole et al., 2013)	SCLC, various adenocarcinomas lymphoma, bowel, kidney cancers (O'Toole et al., 2013)	CSF: normal or with non-specific inflammatory changes MRI: normal or hyperintensities of basal ganglia (may be transient) diffuse leukoencephalopathy (Vigliani et al., 2011)	No effective treatment (O'Toole et al., 2013) Longer survival in patients with SCLC and anti-CRMP5-related encephalitis than those with anti-Hu-related encephalitis (Honnorat et al., 2009)
Paraneoplastic stiff person syndrome	Stiffness mostly in the neck and arms, spinal myoclonus, pruritis Symptoms are asymmetric, distal distribution (Pittock et al., 2005; Murinson and Guarnaccia, 2008)	Amphiphysin (Antoine et al., 1999; Dorresteijn et al. 2002; Ishii et al., 2004) Gephyrin (Butler et al., 2000)	SCLC and breast cancer (Antoine et al., 1999; Dorresteijn et al., 2002; Ishii et al., 2004) Mediastinal cancer (Butler et al., 2000)	EMG: continuous motor unit activity (more prominent in paraspinal muscles – thoracolumbar, rectus abdominis, and proximal limb muscles) Usually, simultaneous involvement of the agonist and antagonist muscle groups are present (Brown and Marsden, 1999)	Corticosteroids, IVIg, plasmapferesis (Brashear and Phillips, 1991; Gordon et al., 1991; Nakamagoe et al., 1995; Dalakas et al., 2001; Meinck 2001; De la Casa-Fages et al. 2013) Tacrolimus at low doses (Nakane et al., 2013) Botulin toxin A, benzodiazepins, pregabalin in the symptomatic treatment (Vasconcelos and Dalakas, 2003; Anagnostou and Zambelis, 2012; Squintani et al., 2012)
Paraneoplastic OMAS in adults	Opsoclonus, myoclonus, and ataxia (Mitchell and Snodgrass, 1990)	Ri (most frequent), anti-Hu, amphiphysin, Yo, CV2/CRMP (Luque et al., 1991; Honnorat et al., 1997; Bataller et al., 2001; Gozzard and Maddison, 2010; Klaas et al., 2012)	Lung, breast, and ovarian cancers, renal cell carcinoma, gastric adenocarcinoma (Luque et al., 1991; Vigliani et al., 2011)	MRI is usually normal; sometimes shows an area of T2-increased signal in the thalamus CSF: usually with mild increases in proteins and a lymphocytic pleocytosis or can be normal (Bataller et al., 2001; Scarff et al., 2011)	Only when malignancy is controlled, patient may benefit from immunomodulatory treatment (corticosteroids or IVIg) (Bataller et al., 2001)
Jaw dystonia and laryngospasm (Pittock et al., 2010)	Jaw dystonia with mouth opening leading to nutritional complications Episodic, recurrent laryngospasm associated with respiratory distress Sometimes brainstem involvement (Pittock et al., 2010)	Ri (Pittock et al., 2010)	Breast cancer (Pittock et al., 2010)	MRI: usually normal or gadolinium enhancement in mesiotemporal lobes, uncus, hemispheric white matter, and pons or hyperintensities of insular cortex (transient), dorsal pons (Pittock et al., 2010)	Immunosuppressants, cytothoxic therapies, and botulinum toxicum (Pittock et al., 2010)

Table 3: Extrapyramidal symptoms in paraneoplastic encephalitis.

Extrapyramidal symptoms	Encephalitis	Antibody	Tumor
Oro-lingual-facial dyskinesias, ballismus, limb and trunk choreoathetosis with oculogyric deviation, opisthotonus, dystonic limb posturing, parkinsonian syndrome, rigidity, myoclonus (Kleinig et al., 2008; Irani et al., 2010a,b; Dalmau et al., 2011)	Anti-NMDAR encephalitis	Anti-NMDAR antibodies (Dalmau et al., 2007)	Ovarian teratoma (Dalmau et al., 2007)
Parkinsonism (hypokinesis, masked face, hypophonia, rigidity, micrographia, tremor) hypokinetic syndrome with a tendency to eye closure and dramatic reduction of verbal output (Dalmau et al., 2004; Matsumoto et al., 2007; Hoffmann et al., 2008)	Anti-MA2-associated encephalitis	Anti-Ma2 antibodies (Dalmau et al., 2004)	Germ-cell tumors, NSCLC (Mathew et al., 2007)
Chorea and myoclonus (Kinirons et al., 2003; Morales La Madrid et al., 2012)	Paraneoplastic limbic encephalitis	Onconeural antibodies (anti-Hu, anti-Ma2/Ta, anti-CV2/CRMP, anti-amphiphysin) Antibodies against surface antigens (anti-NMDAR, anti-VGKC, anti-Ach, anti-DNER, anti-AMPAr, anti-GABA Br) (Lai et al., 2009; Gozzard and Maddison, 2010; Boronat et al., 2011)	SCLC, testicular germ-cell tumors, breast cancer, Hodgkin's lymphoma, teratoma thymoma (Gultekin et al., 2000)

NSCLC, Non-small cell lung cancer.

gain of weight, or sexual dysfunction. Criteria for brainstem encephalitis include cranial neuropathy, nuclear or supranuclear ophthalmoparesis, parkinsonism, dysarthria, or dysphagia (Dalmau et al., 2004). Clinical presentation of paraneoplastic parkinsonism consists of hypokinesis, masked face, hypophonia, rigidity, micrographia, and tremor (Dalmau et al., 2004; Matsumoto et al., 2007; Hoffmann et al., 2008). Severe hypokinetic syndrome with a tendency to eye closure and dramatic reduction of verbal output may also occur (Dalmau et al., 2004). Interestingly, only a subset of patients with antibodies limited to Ma2 develop parkinsonian-hypokinetic features (Dalmau et al., 2004). T2/FLAIR-weighted brain MRI scans often show hyperintensity of the medial temporal lobes, hypothalamus, thalamus, and upper brainstem, sometimes with dye enhancement (Dalmau et al., 2004). CSF examination may reveal increased protein concentration and IgG index elevation (Matsumoto et al., 2007). Patients under 50 years are all men with germ-cell tumors. The group of patients older than 50 years includes both sexes and is associated mostly with non-small cell lung cancer (Mathew et al., 2007). The management of anti-Ma2 encephalitis involves tumor therapy if applicable and immunotherapy. Association between immunosuppression and clinical improvement has not been found; however, it can be effective in some patients. About 30% of patients have neurological improvement, and about a half of them present clinical deterioration (Dalmau et al., 2004). What is noteworthy is that neurological symptoms caused only by Ma2 antibodies may improve or resolve after proper treatment. No neurological improvement and more deaths are observed in patients with Ma1 and Ma3 antibodies. The exact mechanism of this phenomenon is unclear (Rosenfeld et al., 2001).

Paraneoplastic limbic encephalitis

Characteristic features of paraneoplastic limbic encephalitis were mentioned above. Noteworthy is the fact that chorea and myoclonus have also been reported (Kinirons et al., 2003; Morales La Madrid et al., 2012). The disorder can be associated with oncloneural antibodies (anti-Hu, anti-Ma2/Ta, anti-CV2/CRMP, and anti-amphiphysin) and antibodies against surface antigens (anti-NMDAR, anti-VGKC, anti-Ach, anti-DNER, anti-AMPAr, and anti-GABA Br) (Lai et al., 2009; Gozzard and Maddison, 2010; Boronat et al., 2011). Small cell lung cancer and testicular germ-cell tumors are the most frequent neoplasm, but other malignancy like breast cancer, Hodgkin's lymphoma, teratoma,

or thymoma also can be present. Brain MRI usually reveals unilateral or bilateral temporal lobe abnormalities on T2-weighted images or atrophy on T1-weighted scans. CSF analysis may show increased protein level, oligoclonal bands, and pleocytosis with predominant lymphocytes (Gultekin et al., 2000). Response to immunotherapy seems to depend on the type of antibodies (Bataller et al., 2007). Patients with antibodies against cell surface antigens usually present more favorable neurological outcome than those with intracellular ones (Bataller et al., 2007). However, cases of lack of neurological improvement after immunomodulatory treatment in patients with antibodies against cell surface antigens have been described (Graus et al., 2008) (see Table 3).

Conclusions

PMD are rare, autoimmune-mediated, nonmetastatic complications of tumor. Rapid clinical course, inflammatory changes in the CSF, and the presence of serum or CSF onconeuronal antibodies should suggest the diagnosis of PNS/PMD. If PNS/PMD is suspected, prompt screening for tumor is needed. Early diagnosis and proper treatment sometimes leads to neurological improvement and may improve cancer prognosis.

References

Ameli, R., Snow, J., Rakocevic, G., and Dalakas M.C. (2005). A neuropsychological assessment of phobias in patients with stiff person syndrome. Neurology *64*, 1961–1963.

Anagnostou, E. and Zambelis, T. (2012). Botulinum toxin A in anti-GAD positive stiff limb syndrome. Muscle Nerve *46*, 457–458.

Antoine, J.C., Absi, L., Honnorat, J., Boulesteix, J.M., de Brouker, T., Vial, C., Butler, M., De Camilli, P., and Michel, D. (1999). Antiamphiphysin antibodies are associated with various paraneoplastic neurological syndromes and tumors. Arch. Neurol. *56*, 172–177.

Armstrong, M.B., Robertson, P.L., and Castle V.P. (2005). Delayed, recurrent opsoclonus-myoclonus syndrome responding to plasmapheresis. Pediatr. Neurol. *33*, 365–367.

Baets, J., Pals, P., Bergmans, B., Foncke, E., Smets, K., Hauman, H., Vanderwegen, L., and Cras, P. (2006). Opsoclonus-myoclonus syndrome: a clinicopathological confrontation. Acta Neurol. Belg. *106*, 142–146.

Barker, R.A., Revesz, T., Thom, M., Marsden, C.D., and Brown, P. (1998). Review of 23 patients affected by the stiff man syndrome: clinical subdivision into stiff trunk (man) syndrome, stiff limb syndrome, and progressive encephalomyelitis with rigidity. J. Neurol. Neurosurg. Psychiatry *65*, 633–640.

Bataller, L., Graus, F., Saiz, A., and Vilchez, J.J. (2001). Clinical outcome in adult onset idiopathic or paraneoplastic opsoclonus-myoclonus. Brain *124*, 437–443.

Bataller, L., Kleopa, K.A., Wu, G.F., Rossi, J.E., Rosenfeld, M.R, and Dalmau, J. (2007). Autoimmune limbic encephalitis in 39 patients: immunophenotypes and outcomes. J. Neurol. Neurosurg. Psychiatry *78*, 381–385.

Bayreuther, C., Bourg, V., Dellamonica, J., Borg, M., Bernardin, G., and Thomas, P. (2009). Complex partial status epilepticus revealing anti-NMDA receptor encephalitis. Epileptic Disord. *11*, 261–265.

Beck, S., Fuehlhuber, V., Krasenbrink, I., Tschernatsch, M., Kneifel, N., Kirsten, A., Jaeger, C., Kaps, M., Preissner, K.T., Lang, B., et al. (2007). IgG subclass distribution of autoantibodies in pediatric opsoclonus-myoclonus syndrome. J. Neuroimmunol. *185*, 145–149.

Blaes, F., Fuehlhuber, V., Korfei, M., Tschernatsch, M., Behnisch, W., Rostasy, K., Hero, B., Kaps, M., and Preissner, K.T. (2005). Surface-binding autoantibodies to cerebellar neurons in opsoclonus syndrome. Ann. Neurol. *58*, 313–317.

Boronat, A., Sabater, L., Saiz, A., Dalmau, J., and Graus, F. (2011). GABA(B) receptor antibodies in limbic encephalitis and anti-GAD-associated neurologic disorders. Neurology *76*, 795–800.

Brashear, H.R. and Phillips, L.H. 2nd. (1991). Autoantibodies to GABAergic neurons and response to plasmapheresis in stiff-man syndrome. Neurology *41*, 1588–1592.

Brown, P. and Marsden, C.D. (1999). The stiff man and stiff man plus syndromes. J. Neurol. *246*, 648–652.

Brunklaus, A., Pohl, K., Zuberi, S.M., and de Sousa, C. (2011). Outcome and prognostic features in opsoclonus-myoclonus syndrome from infancy to adult life. Pediatrics *128*, 388–394.

Butler, M.H., Hayashi, A., Ohkoshi, N., Villmann, C., Becker, C.M., Feng, G., De Camilli, P., and Solimena, M. (2000). Autoimmunity to gephyrin in stiff-man syndrome. Neuron. *26*, 307–312.

Caviness, J., Forsyth, P., Layton, D., and McPhee, T.J. (1995). The movement disorder of adult opsoclonus. Mov. Disord. *10*, 22–27.

Dalakas, M.C., Fujii, M., Li, M., and McElroy, B. (2000). The clinical spectrum of anti-GAD antibody-positive patients with stiff-person syndrome. Neurology *55*, 1531–1535.

Dalakas, M.C., Fujii, M., Li, M., Lutfi, B., Kyhos, J., and McElroy, B. (2001). High-dose intravenous immune globulin for stiff-person syndrome. N. Engl. J. Med. *345*, 1870–1876.

Dalmau, J., Graus, F., Villarejo, A., Posner, J.B., Blumenthal, D., Thiessen, B., Saiz, A., Meneses, P., and Rosenfeld, M.R. (2004). Clinical analysis of anti-Ma2-associated encephalitis. Brain *127*, 1831–1844.

Dalmau, J., Tüzün, E., Wu, H.Y., Masjuan, J., Rossi, J.E., Voloschin, A., Baehring, J.M., Shimazaki, H., Koide, R., King, D., et al. (2007). Paraneoplastic anti-*N*-methyl-D-aspartate receptor encephalitis associated with ovarian teratoma. Ann. Neurol. *61*, 25–36.

Dalmau, J., Gleichman, A.J., Hughes, E.G., Rossi, J.E., Peng, X., Lai, M., Dessain, S.K., Rosenfeld, M.R., Balice-Gordon, R., and Lynch, D.R. (2008). Anti-NMDA-receptor encephalitis: case series and analysis of the effects of antibodies. Lancet Neurol. *7*, 1091–1098.

Dalmau, J., Lancaster, E., Martinez-Hernandez, E., Rosenfeld, M.R., and Balice-Gordon, R. (2011). Clinical experience and laboratory investigations in patients with anti-NMDAR encephalitis. Lancet Neurol. *10*, 63–74.

Darnell, R.B. and Posner, J.B. (2003). Paraneoplastic syndromes involving the nervous system. N. Engl. J. Med. *349*, 1543–1554.

de Graaff, E., Maat, P., Hulsenboom, E., van den Berg, R., van den Bent, M., Demmers, J., Lugtenburg, P.J., Hoogenraad, C.C., and Sillevis Smitt, P. (2012). Identification of delta/notch-like epidermal growth factor-related receptor as the Tr antigen in paraneoplastic cerebellar degeneration. Ann. Neurol. *71*, 815–824.

De Grandis, E., Parodi, S., Conte, M., Angelini, P., Battaglia, F., Gandolfo, C., Pessagno, A., Pistoia, V., Mitchell, W.G., Pike, M., et al. (2009). Long-term follow-up of neuroblastoma-associated opsoclonus-myoclonus-ataxia syndrome. Neuropediatrics *40*, 103–111.

De la Casa-Fages, B., Anaya, F., Gabriel-Ortemberg, M., and Grandas, F. (2013). Treatment of stiff-person syndrome with chronic plasmapheresis. Mov. Disord. *28*, 396–397.

Derksen, A., Stettner, M., Stöcker, W., and Seitz R.J. (2013). Anti-glycine receptor-related stiff limb syndrome in a patient with chronic lymphocytic leukaemia. Br. Med. J. Case Rep. *20*, 2013.

Dorresteijn, L.D., Kappelle, A.C., Renier, W.O., and Gijtenbeek, J.M. (2002). Antiamphiphysin associated limbic encephalitis: a paraneoplastic presentation of small-cell lung carcinoma. J. Neurol. *249*, 1307–1308.

Geis, C., Beck, M., Jablonka, S., Weishaupt, A., Toyka, K.V., Sendtner, M., and Sommer, C. (2009). Stiff person syndrome associated anti-amphiphysin antibodies reduce GABA associated $[Ca^{2+}]_i$ rise in embryonic motoneurons. Neurobiol. Dis. *36*, 191–199.

Geis, C., Weishaupt, A., Hallermann, S., Grünewald, B., Wessig, C., Wultsch, T., Reif, A., Byts, N., Beck, M., Jablonka, S., et al. (2010). Stiff person syndrome-associated autoantibodies to amphiphysin mediate reduced GABAergic inhibition. Brain *133*, 3166–3180.

Geis, C., Grünewald, B., Weishaupt, A., Wultsch, T., Toyka, K.V., Reif, A., and Sommer, C. (2012). Human IgG directed against amphiphysin induces anxiety behavior in a rat model after intrathecal passive transfer. J. Neural Transm. (Vienna) *119*, 981–985.

Gordon, M.F., Pullman, S., and McDonald, T. (1991). Plasmapheresis in the treatment of stiff-man syndrome. Neurology *41*, 223.

Gorman, M.P. (2010). Update on diagnosis, treatment, and prognosis in opsoclonusmyoclonus-ataxia syndrome. Curr. Opin. Pediatr. *22*, 745–750.

Gozzard, P. and Maddison, P. (2010). Which antibody and which cancer in which paraneoplastic syndromes. Pract. Neurol. *10*, 260–270.

Graus, F., Keime-Guibert, F., Rene, R., Benyahia, B., Ribalta, T., Ascaso, C., Escaramis, G., and Delattre, J.Y. (2001). Anti-Hu-associated paraneoplastic encephalomyelitis: analysis of 200 patients. Brain *124*, 1138–1148.

Graus, F., Saiz, A., Lai, M., Bruna, J., López, F., Sabater, L., Blanco, Y., Rey, M.J., Ribalta, T., and Dalmau, J. (2008). Neuronal surface antigen antibodies in limbic encephalitis: clinical-immunologic associations. Neurology *71*, 930–936.

Greenlee, J.E., Clawson, S.A., Hill, K.E., Wood B., Clardy, S.L., Tsunoda, I., and Carlson, N.G. (2015). Anti-Yo antibody uptake and interaction with its intracellular target antigen causes Purkinje cell death in rat cerebellar slice cultures: a possible mechanism for paraneoplastic cerebellar degeneration in humans with gynecological or breast cancers. PLoS One *10*, e0123446.

Gultekin, S.H., Rosenfeld, M.R., Voltz, R., Eichen, J., Posner, J.B., and Dalmau, J. (2000). Paraneoplastic limbic encephalitis: neurological symptoms, immunological findings and tumour association in 50 patients. Brain *123*, 1481–1494.

Hoffmann, L.A., Jarius, S., Pellkofer, H.L., Schueller, M., Krumbholz, M., Koenig, F., Johannis, W., la Fougere, C., Newman, T., Vincent, A., et al. (2008). Anti-Ma and anti-Ta associated paraneoplastic neurological syndromes: 22 newly diagnosed patients and review of previous cases. J. Neurol. Neurosurg. Psychiatry *79*, 767–773.

Honnorat, J., Cartalat-Carel, S., Ricard, D., Camdessanche, J.P., Carpentier, A.F., Rogemond, V., Chapuis, F., Aguera, M., Decullier, E., Duchemin, A.M., et al. (2009). Onco-neural antibodies and tumour type determine survival and neurological symptoms in paraneoplastic neurological syndromes with Hu or CV2/CRMP5 antibodies. J. Neurol. Neurosurg. Psychiatry *80*, 412–416.

Honnorat, J., Trillet, M., Antoine, J.C., Aguera, M., Dalmau, J., and Graus, F. (1997). Paraneoplastic opsomyoclonus, cerebellar ataxia and encephalopathy associated with anti-Purkinje cell antibodies. J. Neurol. *244*, 333–335.

Hutchinson, M., Waters, P., McHugh, J., Gorman, G., O'Riordan, S., Connolly, S., Hager, H., Yu, P., Becker, C.M., and Vincent, A. (2008). Progressive encephalomyelitis, rigidity, and myoclonus: a novel glycine receptor antibody. Neurology *71*, 1291–1292.

Iizuka, T., Yoshii, S., Kan, S., Hamada, J., Dalmau, J., Sakai, F., and Mochizuki, H. (2010). Reversible brain atrophy in anti-NMDA receptor encephalitis: a long-term observational study. J. Neurol. *257*, 1686–1691.

Irani, S.R., Alexander, S., Waters, P., Kleopa, K.A., Pettingill, P., Zuliani, L., Peles, E., Buckley, C., Lang, B., and Vincent, A. (2010a). Antibodies to Kv1 potassium channel-complex proteins leucine-rich, glioma inactivated 1 protein and contactin-associated protein-2 in limbic encephalitis, Morvan's syndrome and acquired neuromyotonia. Brain *133*, 2734–2748.

Irani, S.R., Bera, K., Waters, P., Zuliani, L., Maxwell, S., Zandi M.S., Friese M.A., Galea, I., Kullmann, D.M., Beeson, D., et al. (2010b). *N*-methyl-D-aspartate antibody encephalitis: temporal progression of clinical and paraclinical observations in a predominantly nonparaneoplastic disorder of both sexes. Brain *133*, 1655–1667.

Ishii, A., Hayashi, A., Ohkoshi, N., Matsuno, S., and Shoji, S. (2004). Progressive encephalomyelitis with rigidity associated with antiamphiphysin antibodies. J. Neurol. Neurosurg. Psychiatry *75*, 661–662.

Keime-Guibert, F., Graus, F., Fleury, A., René, R., Honnorat, J., Broet, P., and Delattre, J.Y. (2000). Treatment of paraneoplastic neurological syndromes with antineuronal antibodies (anti-Hu, anti-Yo) with a combination of immunoglobulins, cyclophosphamide, and methylprednisolone. J. Neurol. Neurosurg. Psychiatry *68*, 479–482.

Kinirons, P., Fulton, A., Keoghan, M., Brennan, P., Farrell, M.A., and Moroney, J.T. (2003). Paraneoplastic limbic encephalitis (PLE) and chorea associated with CRMP-5 neuronal antibody. Neurology *61*, 1623–1624.

Klaas, J.P., Ahlskog, E., Pittock, S.J., Matsumoto, J.Y., Aksamit, A.J., Bartleson, J.D., Kumar, R., McEvoy, K.F., and McKeon, A. (2012). Adult-onset opsoclonus-myoclonus syndrome. Arch. Neurol. *69*, 1598–1607.

Kleinig, T.J., Thompson, P.D., Matar, W., Duggins, A., Kimber, T.E., Morris, J.G., Kneebone, C.S., and Blumbergs, P.C. (2008). The distinctive movement disorder of ovarian teratoma-associated encephalitis. Mov. Disord. *23*, 1256–1261.

Kyskan, R., Chapman, K., Mattman, A., and Sin, D. (2013). Antiglycine receptor antibody and encephalomyelitis with rigidity and

myoclonus (PERM) related to small cell lung cancer. Br. Med. J. Case Rep. *21*, 2013.

Lai, M., Hughes, E.G., Peng, X., Zhou, L., Gleichman, A.J., Shu, H., Matà, S., Kremens, D., Vitaliani, R., Geschwind, M.D., et al. (2009). AMPA receptor antibodies in limbic encephalitis alter synaptic receptor location. Ann. Neurol. *65*, 424–434.

Lai, M., Huijbers, M.G., Lancaster, E., Graus, F., Bataller, L., Balice-Gordon, R., Cowell, J.K., and Dalmau, J. (2010). Investigation of LGI1 as the antigen in limbic encephalitis previously attributed to potassium channels: a case series. Lancet Neurol. *9*, 776–785.

Lancaster, E. and Dalmau, J. (2012). Neuronal autoantigens – pathogenesis, associated disorders and antibody testing. Nat. Rev. Neurol. *8*, 380–390.

Lancaster, E., Huijbers, M.G., Bar, V., Boronat, A., Wong, A., Martinez-Hernandez, E., Wilson, C., Jacobs, D., Lai, M., Walker, R.W., et al. (2011). Investigations of Caspr2, an autoantigen of encephalitis and neuromyotonia. Ann. Neurol. *69*, 303–311.

Lancaster, E., Lai, M., Peng, X., Hughes, E., Constantinescu, R., Raizer, J., Friedman, D., Skeen, M.B., Grisold, W., Kimura, A., et al. (2010). Antibodies to the $GABA_B$ receptor in limbic encephalitis with seizures: case series and characterisation of the antigen. Lancet Neurol. *9*, 67–76.

Lancaster, E., Martinez-Hernandez, E., Titulaer, M.J., Boulos, M., Weaver, S., Antoine, J.C., Liebers, E., Kornblum, C., Bien, C.G., Honnorat, J., et al. (2011). Antibodies to metabotropic glutamate receptor 5 in the Ophelia syndrome. Neurology *77*, 1698–1701.

Lorish, T.R., Thorsteinsson, G., and Howard, F.M. (1989). Stiff-man syndrome updated. Mayo Clin. Proc. *64*, 629–636.

Luque, F.A., Furneaux, H.M., Ferziger, R., Rosenblum, M.K., Wray, S.H., Schold, S.C. Jr, Glantz, M.J., Jaeckle, K.A., Biran, H., and Lesser, M. (1991). Anti-Ri: an antibody associated with paraneoplastic opsoclonus and breast cancer. Ann. Neurol. *29*, 241–251.

Manto, M.U., Laute, M.A., Aguera, M., Rogemond, V., Pandolfo, M., and Honnorat, J. (2007). Effects of antiglutamic acid decarboxylase antibodies associated with neurological diseases. Ann. Neurol. *61*, 544–551.

Mas, N., Saiz, A., Leite M.I., Waters, P., Baron, M., Castaño, D., Sabater, L., Vincent, A., and Graus F. (2011). Antiglycine-receptor encephalomyelitis with rigidity. J. Neurol. Neurosurg. Psychiatry *82*, 1399–1401.

Mathew, R.M., Vandenberghe, R., Garcia-Merino, A., Yamamoto, T., Landolfi, J.C., Rosenfeld, M.R., Rossi, J.E., Thiessen, B., Dropcho, E.J., and Dalmau, J. (2007). Orchiectomy for suspected microscopic tumor in patients with anti-Ma2-associated encephalitis. Neurology *68*, 900–905.

Matsumoto, L., Yamamoto, T., Higashihara, M., Sugimoto, I., Kowa, H., Shibahara, J., Nakamura, K., Shimizu, J., Ugawa, Y., Goto, J., et al. (2007). Severe hypokinesis caused by paraneoplastic anti-Ma2 encephalitis associated with bilateral intratubular germ-cell neoplasm of the testes. Mov. Disord. *22*, 728–731.

Meinck, H.M. (2001). Stiff man syndrome. CNS Drugs *15*, 515–526.

Meinck, H.M. and Thompson, P.D. (2002). Stiff man syndrome and related conditions. Mov. Disord. *17*, 853–866.

Mitchell, W.G. and Snodgrass, S.R. (1990). Opsoclonus-ataxia due to childhood neural crest tumors: a chronic neurologic syndrome. J. Child Neurol. *5*, 153–158.

Mitchell, W.G., Brumm, V.L., Azen, C.G., Patterson, K.E., Aller, S.K., and Rodriguez, J. (2005). Longitudinal neurodevelopmental evaluation of children with opsoclonus-ataxia. Pediatrics *116*, 901–907.

Morales La Madrid, A., Rubin, C.M., Kohrman, M., Pytel, P., and Cohn, S.L. (2012). Opsoclonus-myoclonus and anti-Hu positive limbic encephalitis in a patient with neuroblastoma. Pediatr. Blood Cancer *58*, 472–474.

Murinson, B.B. and Guarnaccia, J.B. (2008). Stiff-person syndrome with amphiphysin antibodies: distinctive features of a rare disease. Neurology *71*, 1955–1958.

Nakamagoe, K., Ohkoshi, N., Hayashi, A., Hisahara, S., and Shoji, S. (1995). Marked clinical improvement by plasmapheresis in a patient with stiff-man syndrome: a case with a negative anti-GAD antibody. Rinsho Shinkeigaku *35*, 897–900.

Nakane, S., Fujita, K., Shibuta, Y., Matsui, N., Harada, M., Urushihara, R., Nishida, Y., Izumi, Y., and Kaji, R. (2013). Successful treatment of stiff person syndrome with sequential use of tacrolimus. J. Neurol. Neurosurg. Psychiatry *84*, 1177–1180.

O'Toole, O., Lennon, V.A., Ahlskog, J.E., Matsumoto, J.Y., Pittock, S.J., Bower, J., Fealey, R., Lachance, D.H., and McKeon, A. (2013). Autoimmune chorea in adults. Neurology *80*, 1133–1144.

Orange, D., Frank, M., Tian, S., Dousmanis, A., Marmur, R., Buckley, N., Parveen, S., Graber, J.J., Blachère, N., and Darnell RB. (2012). Cellular immune suppression in paraneoplastic neurologic syndromes targeting intracellular antigens. Arch. Neurol. *9*, 1132–1140.

Pittock, S.J., Lucchinetti, C.F., Parisi, J.E., Benarroch, E.E., Mokri, B., Stephan, C.L., Kim, K.K., Kilimann, M.W., and Lennon, V.A. (2005). Amphiphysin autoimmunity: paraneoplastic accompaniments. Ann. Neurol. *58*, 96–107.

Pittock, S.J., Parisi, J.E., McKeon, A., Roemer, S.F., Lucchinetti, C.F., Tan, K.M., Keegan, B.M., Hunter, S.F., Duncan, P.R., Baehring, J.M., et al. (2010) Paraneoplastic jaw dystonia and laryngospasm with antineuronal nuclear autoantibody type 2 (anti-Ri). Arch. Neurol. *67*, 1109–1115.

Posner, J.B. and Davines, F.A. (1995). Paraneoplastic syndromes. Neurol. Complications Cancer, 353–385.

Pranzatelli, M.R. (1996). The immunopharmacology of the opsoclonus myoclonus syndrome. Clin. Neuropharmacol. *19*, 1–47.

Pranzatelli, M.R., Tate, E.D., Swan, J.A., Travelstead, A.L., Colliver, J.A., Verhulst, S.J., Crosley, C.J., Graf, W.D., Joseph, S.A., Kelfer, H.M., et al. (2010). B cell depletion therapy for new onset opsoclonus-myoclonus. Mov. Disord. *25*, 238–242.

Pranzatelli, M.R., Tate, E.D., Shenoy, S., and Travelstead, A.L. (2012). Ofatumumab for a rituximaballergic child with chronic-relapsing paraneoplastic opsoclonus myoclonus. Pediatr. Blood Cancer *58*, 988–991.

Psimaras, D., Carpentier, A.F., and Rossi, C. (2010). Cerebrospinal fluid study in paraneoplastic syndromes. J. Neurol. Neurosurg. Psychiatry *81*, 42–45.

Raju, R., Rakocevic, G., Chen, Z., Hoehn, G., Semino-Mora, C., Shi, W., Olsen, R., and Dalakas, M.C. (2006). Autoimmunity to $GABA_A$ receptor associated protein in stiff-person syndrome. Brain *129*, 3270–3276.

Rakocevic, G., Raju, R., and Dalakas, M.C. (2004). Anti-glutamic acid decarboxylase antibodies in the serum and cerebrospinal fluid of patients with stiff-person syndrome: correlation with clinical severity. Arch. Neurol. *61*, 902–904.

Rojas, I., Graus, F., Keime-Guibert, F., Reñé, R., Delattre, J.Y., Ramón, J.M., Dalmau, J., and Posner, J.B. (2000). Long-term clinical

outcome of paraneoplastic cerebellar degeneration and anti-Yo antibodies. Neurology *55*, 713–715.

Rosenfeld, M.R., Eichen, J.G., Wade, D.F., Posner, J.B., and Dalmau, J. (2001). Molecular and clinical diversity in paraneoplastic immunity to Ma proteins. Ann. Neurol. *50*, 339–348.

Saiz, A., Blanco, Y., Sabater, L., González, F., Bataller, L., Casamitjana, R., Ramió-Torrentà, L., and Graus, F. (2008). Spectrum of neurological syndromes associated with glutamic acid decarboxylase antibodies: diagnostic clues for this association. Brain *131*, 2553–2563.

Scarff, J.R., Iftikhar, B., Tatugade, A., Choi, J., and Lippmann, S. (2011) Opsoclonus myoclonus. Innov. Clin. Neurosci. *8*, 29–31.

Shams'ili, S., Grefkens, J., de Leeuw, B., van den Bent, M., Hooijkaas, H., van der Holt, B., Vecht, C., and Sillevis Smitt, P. (2003). Paraneoplastic cerebellar degeneration associated with antineuronal antibodies: analysis of 50 patients. Brain *126*, 1409–1418.

Shams'ili, S., de Beukelaar, J., Gratama, J.W., Hooijkaas, H. van den Bent, M., van 't Veer, M., and Sillevis Smitt, P. (2006). An uncontrolled trial of rituximab for antibody associated paraneoplastic neurological syndromes. J. Neurol. *253*, 16–20.

Sillevis Smitt, P.A., Manley, G.T., and Posner, J.B. (1995). Immunization with the paraneoplastic encephalomyelitis antigen HuD does not cause neurologic disease in mice. Neurology *45*, 1873–1878.

Sillevis Smitt, P.A., Grefkens, J., de Leeuw, B., van den Bent, M., van Putten, W., Hooijkaas, H., Vecht, C. (2002). Survival and outcome in 73 anti-Hu positive patients with paraneoplastic encephalomyelitis/sensory neuronopathy. J. Neurol. *249*, 745–753.

Sommer, C., Weishaupt, A., Brinkhoff, J., Biko, L., Wessig, C., Gold, R., and Toyka, K.V. (2005). Paraneoplastic stiff-person syndrome: passive transfer to rats by means of IgG antibodies to amphiphysin. Lancet *365*, 1406–1411.

Spay, A.J. and Chen, R. (2006). Rigidity and spasms from autoimmune encephalomyelopathies: stiff-person syndrome. Muscle Nerve *34*, 677–690.

Squintani, G., Bovi, T., Ferigo, L., Musso, A.M., Ottaviani, S., Moretto, G., Morgante, F., and Tinazzi, M. (2012). Efficacy of pregabalin in a case of stiff-person syndrome: clinical and neurophysiological evidence. J. Neurol. Sci. *15*, 314.

Stich, O., Jarius, S., Kleer B., Rasiah, C., Voltz, R., and Rauer, S. (2007). Specific antibody index in cerebrospinal fluid from patients with central and peripheral paraneoplastic neurological syndromes. J. Neuroimmunol. *183*, 220–224.

Tanaka, K., Tanaka, M., Igarashi, S., Onodera, O., Miyatake, T., and Tsuji, S. (1995). Trial to establish an animal model of paraneoplastic cerebellar degeneration with anti-Yo antibody. 2. Passive transfer of murine mononuclear cells activated with recombinant Yo protein to paraneoplastic cerebellar degeneration lymphocytes in severe combined immunodeficiency mice. Clin. Neurol. Neurosurg. *97*, 101–105.

Thompson, P.D. (1994). Stiff people. Movement Disorders 3. C.D. Marsden and S. Fahn, eds. (Oxford, UK: Butterworth-Heinemann), pp. 373–405.

Titulaer, M.J., Soffietti, R., Dalmau, J., Gilhus, N.E., Giometto, B., Graus, F., Grisold, W., Honnorat, J., Sillevis Smitt, P.A., Tanasescu, R., et al. (2011). Screening for tumours in paraneoplastic syndromes: report of an EFNS task force. Eur. J. Neurol. *18*, 19–27.

van Broekhoven, F., de Graaf, M.T., Bromberg, J.E., Hooijkaas, H., van den Bent, M.J., de Beukelaar, J.W., Khan, N.A., Gratama, J.W., van der Geest, J.N., Frens, M., et al. (2010). Human chorionic gonadotropin treatment of anti-Hu-associated paraneoplastic neurological syndromes. J. Neurol. Neurosurg. Psychiatry *81*, 1341–1344.

Vasconcelos, O.M. and Dalakas, M.C. (2003). Stiff-person syndrome. Curr. Treat. Options Neurol. *5*, 79–90.

Vernino, S. and Lennon, V.A. (2004). Autoantibody profiles and neurological correlations of thymoma. Clin. Cancer Res. *10*, 7270–7275.

Uchuya, M., Graus, F., Vega, F., and Rene, R. (1996). Intravenous immunoglobulin treatment in paraneoplastic neurological syndromes with antineuronal autoantibodies. J. Neurol. Neurosurg. Psychiatry *60*, 388–392.

Vigliani, M.C., Honnorat, J., Antoine, J.C., Vitaliani, R., Giometto, B., Psimaras, D., Franchino, F., Rossi, C., and Graus, F. (2011). Chorea and related movement disorders of paraneoplastic origin: the PNS EuroNetwork experience. J. Neurol. *258*, 2058–2068.

Wilken, B., Baumann, M., Bien, C.G., Hero, B., Rostasy, K., and Hanefeld, F. (2008) Chronic relapsing opsoclonus-myoclonus syndrome: combination of cyclophosphamide and dexamethasone pulses. Eur. J. Paediatr. Neurol. *12*, 51–55.

Wong, A. (2007). An update on opsoclonus. Curr. Opin. Neurol. *20*, 25–31.