Paraneoplastic Movement Disorders

Shyamal H. Mehta, MD, PhD, John C. Morgan, MD, PhD, and Kapil D. Sethi, MD, FRCP (UK)

Corresponding author
Shyamal H. Mehta, MD, PhD
Movement Disorders Program, Department of Neurology, 1429 Harper Street, HF-1121, Augusta, GA 30912, USA.
E-mail: shmehta@mcg.edu

Current Neurology and Neuroscience Reports 2009, **9**:285–291
Current Medicine Group LLC ISSN 1528-4042

Neurologic paraneoplastic syndromes (NPSs) result from damage to the nervous system due to the remote effects of cancer not related to metastasis, infection, or metabolic derangements. NPSs are rare, affecting 1 in 10,000 patients with cancer. Pathogenesis is likely related to the immune mechanisms: normal neural tissue is mistakenly attacked due to the similarity in the onconeural antigens expressed by the tumor cells. Among the various "classic" and other NPSs, this review focuses on paraneoplastic movement disorders, including ataxia due to cerebellar degeneration, stiff-person syndrome, opsoclonus–myoclonus syndrome, chorea, parkinsonism, and tremor. The recently described syndrome of paraneoplastic anti–*N*-methyl-D-aspartate receptor encephalitis is also included, given that these patients have complex movements such as stereotypies and dyskinesias in addition to psychiatric symptoms, altered sensorium, and other neurologic signs. Although variable, treatment and prognosis of NPSs rely heavily on treatment of the underlying malignancy and immunotherapy.

Introduction

Paraneoplastic syndromes are defined as dysfunction of an organ or tissue caused by a malignant neoplasm but not directly related to invasion of the affected organ or tissue by the primary tumor or its metastasis [1]. In the context of neurology, these rare syndromes result from damage to the nervous system in the setting of cancer but remote from the site of tumor and not related to metastasis, infection, or metabolic derangements otherwise associated with cancer; they may affect the central as well as the peripheral nervous system [2]. The underlying pathogenesis of these disorders is likely related to the immune system mechanisms—normal neural tissue is mistakenly attacked due to the similarity in the onconeural antigens expressed by the tumor cells. Autoimmune dysfunction may affect one particular site or a single cell type or have diffuse involvement, affecting multiple cell types.

Neurologic paraneoplastic syndromes (NPSs) are rare accompaniments of cancer, occurring in about 0.01% of cancer patients [2]; however, their true incidence is difficult to discern because they are frequently misdiagnosed and underdiagnosed due to their rarity. The frequency of NPSs depends on the cancer associated with it (eg, thymoma is common in patients with myasthenia gravis, and symptoms of myasthenia infrequently improve after thymectomy). NPSs can also occur in the absence of (diagnosed) cancer. Often, the neurologic disorder develops before the cancer becomes clinically overt, making the diagnosis extremely challenging [3]. A classic presentation of NPSs in the absence of a known malignancy should prompt a thorough workup and continued follow-up so that an occult cancer is not missed.

In the past few years, several antibodies associated with NPS have been discovered. These paraneoplastic antibodies are directed against antigens expressed by both the tumor and the nervous system, implicating immune mechanisms in the pathogenesis of NPSs. However, because paraneoplastic antibodies are detected in less than 50% patients with NPSs, the apparent absence of paraneoplastic antibodies does not rule out the diagnosis of an NPS. Also, the presence of antibodies does not confer a disease, because some paraneoplastic antibodies are common in cancer patients without an NPS [4]. To further define the diagnostic criteria for NPSs, a panel reviewed the existing evidence and made recommendations in 2004 [5]. The panel suggested that there should be two levels of diagnostic evidence to define a neurologic syndrome as paraneoplastic: *definite* and *possible,* and a diagnosis of definite or possible NPS could be reached based on a set of criteria (Table 1) [5].

Paraneoplastic syndromes affecting the nervous system can involve the central (eg, presenting as encephalitis or cerebellar degeneration) or the peripheral nervous system (eg, presenting as a neuropathy). This article focuses on paraneoplastic syndromes that cause movement disorders (Table 2).

Paraneoplastic Ataxia

Paraneoplastic cerebellar degeneration (PCD) is one of the well-characterized classic NPSs. Neurologic symptoms are sometimes preceded by prodromal symptoms, such as

Table 1. Diagnostic criteria for neurologic paraneoplastic syndromes*

Definite neurologic paraneoplastic syndrome
A classic syndrome and cancer that develops within 5 years of the diagnosis of the neurologic disorder
A nonclassic syndrome that resolves or significantly improves after cancer treatment without concomitant immunotherapy, provided that the syndrome is not susceptible to spontaneous remission
A nonclassic syndrome with onconeural antibodies (well characterized or not) and cancer that develops within 5 years of the diagnosis of the neurologic disorder
A neurologic syndrome (classic or not) with well-characterized onconeural antibodies (anti-Hu, anti-Yo, anti-CV2, anti-Ri, anti-Ma2, or anti-amphiphysin) and no cancer
Possible neurologic paraneoplastic syndrome
A classic syndrome with no onconeural antibodies or cancer but a high risk of having an underlying tumor
A neurologic syndrome (classic or not) with partially characterized onconeural antibodies and no cancer
A nonclassic syndrome with no onconeural antibodies but with cancer present within 2 years of diagnosis

*The criteria were compiled by an international panel of neurologists [5].

Table 2. Paraneoplastic movement disorders

Ataxia (ie, paraneoplastic cerebellar degeneration)
Stiff-person syndrome
Opsoclonus–myoclonus syndrome
Chorea
Parkinsonism
Tremor

Table 3. Differential diagnosis of selected paraneoplastic movement disorders

Paraneoplastic ataxia
Toxins: drugs, alcohol, medications
Postinfectious cerebellitis
Posterior fossa tumor
Paraneoplastic stiff-person syndrome
Tetanus
Hyperekplexia
Tonic spasms of multiple sclerosis
Strychnine poisoning
Progressive encephalomylitis with rigidity
Paraneoplastic chorea
Drug-induced chorea
Metabolic chorea: hypoglycermia/hyperglycemia, hyperthyroidism, renal failure
Infectious chorea: HIV, Sydenham's chorea
Neuroacanthocytosis
Wilson's disease

a viral-like illness, dizziness, nausea, or vomiting followed by cerebellar symptoms of ataxia, nystagmus (sometimes opsoclonus), and dysarthria [6]. Initially, the findings on MRI may be normal or may show cortical/meningeal enhancement. However, in the later stages, the MRI may be normal and may show cerebellar atrophy. Fluorodeoxyglucose positron emission tomography scanning shows hypermetabolism early in the disease, which changes to hypometabolism as the disease advances [7•].

The histopathological hallmark of PCD is severe loss of Purkinje cells associated with inflammatory infiltrates in the cerebellar cortex, deep cerebellar nuclei, and inferior olivary nuclei [7•]. Evidence seems to suggest that cytotoxic T cells are involved in PCD. A recent report revealed infiltration of $CD8^+$ T cells in and around the dentate nucleus in addition to severe loss of Purkinje cells. A decrease of neurons in the dentate nucleus suggests the possibility of the dentate nucleus being primarily attacked followed by Purkinje cell loss in PCD [8].

Conditions to be considered in the differential diagnosis of paraneoplastic cerebellar degeneration are listed in Table 3.

Malignancies commonly associated with PCD include breast and ovarian cancer, small cell lung cancer (SCLC), and Hodgkin disease. Different onconeural antibodies are associated with cancers causing the syndrome. Breast, ovarian, and other gynecological malignancies are typically associated with anti-Yo antibodies. Anti-Yo antibodies are the most common paraneoplastic antibodies found in PCD [9]. They are directed against the cdr2 antigen expressed by Purkinje cells, resulting in their destruction. The irreversible Purkinje cell loss causes predominantly cerebellar symptoms and significant long-term disability. To improve prognosis, early diagnosis, immunotherapy, and cancer treatment are crucial in anti-Yo antibody–associated PCD. There are a few reports in the literature of significant amelioration of neurologic symptoms with intravenous immune globulin (IVIG). Neurologic outcomes were better with early treatment, and most patients who improved were treated within 1 month of symptom onset and usually received concurrent cancer therapy; treatment between 1 and 3 months resulted in stable disease, and treatment after 3 months usually had a poor outcome [10,11].

Anti-Tr antibodies in the setting of Hodgkin disease are also associated with PCD. Interestingly, the anti-Tr antibodies either completely disappear or in some patients are only found in the cerebrospinal fluid (CSF) after successful treatment of the underlying cancer [12]. Patients with anti-Tr antibodies have a better prognosis than patients with Anti-Yo antibody–associated PCD [13].

PCD also occurs with lung cancer (usually SCLC). In a recent study, SCLC and malignant thymoma were both associated with CV2/CRMP5 antibodies. These patients presented with cerebellar ataxia, chorea, uveo-retinal symptoms, and myasthenic syndrome (Lambert-Eaton myasthenic syndrome [LEMS] or myasthenia gravis) [14••]. Other antibodies, such as Zic4, Ma2, and VGCC, are present in nearly 40% of patients with PCD and lung cancer (usually SCLC) [3]. Although anti-Hu antibodies are predominantly associated with limbic encephalitis, cerebellar symptoms in SCLC have been noted. Esposito et al. [15] have reported a case of successful treatment with rituximab in a patient with anti-Hu antibody PCD with SCLC.

Paraneoplastic Stiff-Person Syndrome

Stiff-person syndrome (SPS) is a rare neurologic condition associated with progressively worsening stiffness and stimulus-sensitive spasms mainly in the axial and limb musculature. The rigidity is caused by continuous motor unit activity in the affected muscles that is detectable on electromyogram (EMG). The etiology of SPS is primarily autoimmune and typically associated with antibodies to glutamic acid decarboxylase (anti-GAD antibodies) and diabetes mellitus type 1. Diagnosis of SPS is made on the basis of clinical features, EMG findings, and an excellent response to diazepam. However, 5% to 10% of cases may be of paraneoplastic etiology secondary to an underlying cancer (more commonly breast adenocarcinoma). The differential diagnosis of paraneoplastic SPS is shown in Table 3. Although paraneoplastic and nonparaneoplastic SPS are clinically similar, advanced age at onset of symptoms, rapid progression, and poor response to diazepam distinguish paraneoplastic from nonparaneoplastic SPS [16].

Paraneoplastic SPS is not commonly associated with anti-GAD antibodies. Instead, studies in women with breast cancer and SPS showed a novel antibody directed against a 128-kDa synaptic vesicle–associated protein called amphiphysin [17]. A recent report of 11 patients with amphiphysin antibody–associated SPS showed that this syndrome is strongly associated with advanced age, cervical region stiffness, female sex, breast cancer (10 of the 11 patients had breast cancer), and a partial response to high-dose benzodiazepines, confirming previous observations regarding paraneoplastic SPS [18•]. Amphiphysin antibodies are a useful screening tool for paraneoplastic SPS because they are rarely seen in cancer patients without a neurologic deficit. However, they are not specific for paraneoplastic SPS and are associated with a wide variety of neurologic syndromes (eg, LEMS, encephalomyelitis, neuropathy) and tumors [19].

Although breast cancer is more commonly associated with paraneoplastic SPS, cancers such as thymoma, myeloma, Hodgkin disease, and lung cancer also have been reported to cause paraneoplastic SPS [20]. Similarly, although amphiphysin antibody–positive paraneoplastic SPS is more common, reports of other antibodies associated with paraneoplastic SPS exist. GAD-positive paraneoplastic SPS in patients with renal cell carcinoma, thymoma, myeloma, and Hodgkin disease have been reported [20]. A patient with paraneoplastic SPS and metastatic lung adenocarcinoma and anti-Ri antibodies has been reported [21]. Butler et al. [22] reported on high-titer autoantibodies directed against gephyrin in a patient with SPS and mediastinal cancer.

As with other NPSs, treatment primarily involves management of the underlying tumor. Symptomatic treatment with benzodiazepines in idiopathic SPSs is more fruitful than in paraneoplastic SPSs. Instead, immunotherapy with steroids, cyclophosphamide, plasmapheresis, and IVIG has been reported [20]. IVIG has proven to be effective in nonparaneoplastic SPSs in two placebo-controlled trials, but the evidence in paraneoplastic SPSs is less substantial—only case reports exist [9].

A syndrome known as progressive encephalomyelitis with rigidity has also been reported and is sometimes used interchangeably with SPS. Clinically, in addition to the limb and truncal rigidity seen in SPS, these patients have brainstem signs and hyperekplexia [16]. There is debate as to whether progressive encephalomyelitis with rigidity represents a different disease or is in the spectrum of SPSs, because about 80% of patients may have anti-GAD antibodies [16]. It may also be paraneoplastic with anti-amphiphysin antibodies.

Paraneoplastic Opsoclonus–Myoclonus Syndrome

Opsoclonus–myoclonus syndrome (OMS) is the acute or subacute development of chaotic, high-amplitude, multidirectional, involuntary eye movements (opsoclonus) with sudden jerky movements of the body, including the limbs (myoclonus). Sometimes these movements may be associated with ataxia, and the syndrome is then referred to as opsoclonus–myoclonus–ataxia syndrome (OMAS).

Pediatric OMS is paraneoplastic in about 40% of cases and is commonly associated with neuroblastoma, although only about 2% to 3% of patients with neuroblastoma develop OMS [23]. It has been difficult to isolate specific paraneoplastic antibodies associated with OMS and neuroblastoma. However, anti-Hu, α-enolase, IgG class antibodies have been reported in the past and, more recently, specific binding of autoantibodies to the surface of neuroblastoma cells and cerebellar granular neurons have been found, suggesting that autoimmunity may play a role in the pathogenesis of OMS in neuroblastoma

[24]. Immunotherapy in children with neuroblastoma and OMS seems to be the mainstay of therapy, with a favorable prognosis for resolution of symptoms. Improvement in symptoms with steroids, IVIG, rituximab, and adrenocorticotrophic hormone suggests transient antibody-mediated dysfunction as opposed to permanent neuronal damage [9]. In many centers, children are treated with prednisone (2 mg/kg/d) and monthly IVIG (2 g/kg at induction), followed by a monthly maintenance dose of 1 g/kg. If symptoms improve, prednisone is tapered off in the next 2 to 3 months. Otherwise, if relapses occur, the dose of IVIG and prednisone is increased. Currently, the Children's Oncology Group at the National Cancer Institute is conducting a randomized multicenter clinical trial to determine whether cyclophosphamide and prednisone with or without IVIG is reasonable baseline standard therapy for children with neuroblastoma-associated OMS/OMAS [25•].

In adults, 20% of OMS cases are paraneoplastic, with 70% of those being secondary to breast and lung cancer [26]. In patients with breast cancer, paraneoplastic OMS may be associated with anti-Ri antibodies. However, in many adults with OMS no autoantibodies are detected. In one study, serum from 12 of 14 patients with paraneoplastic OMS showed no cross-reactivity to rat or human brainstem or cerebellum, lacked specific antineuronal antibodies (Hu, Yo, Ri, Tr, GAD, amphiphysin, or CV2), and did not contain antibodies to voltage-gated calcium channels. The two exceptions were one patient with breast cancer and anti-Ri antibodies and another patient with SCLC and anti-Hu and anti-amphiphysin antibodies [27]. In addition to these relatively common associations, paraneoplastic OMS and OMAS have been seen with gastrointestinal tract lymphoma [28], benign ovarian teratoma [29], melanoma [30], esthesioneuroblastoma [31], non-Hodgkin lymphoma [26], and other conditions. Management of adult paraneoplastic OMS/OMAS involves treatment of the primary tumor. In contrast to children, no clear advantage of immunotherapy in adults with OMS has been demonstrated, although some individuals have responded to IVIG, steroids, immunosuppressants, and plasma adsorption [25•]. Symptomatic treatment of the eye movements could be tried with propranolol, benzodiazepines, thiamine, and baclofen [32], and myoclonus can be treated with typical antimyoclonic agents, such as clonazepam or levetiracetam.

The course and prognosis in children with neuroblastoma and opsoclonus usually involves resolution with or without treatment, but multiple relapses can occur and developmental sequelae such as motor, speech, and language deficits are common [25•]. Adults with paraneoplastic OMS/OMAS have a more severe course despite immunotherapy, and the mortality rate is high in patients whose tumors are not treated. Most patients who undergo treatment for underlying tumors have complete or partial neurologic recovery [27].

Paraneoplastic Chorea

Even though paraneoplastic chorea is rare, Vernino et al. [33] have described 16 cancer patients with chorea, 11 of whom had chorea as their initial and most prominent symptom. Other reports of chorea as a part of a multifocal syndrome with encephalopathy and ataxia in association with cancer also exist [34,35]. Based on various case reports, it seems that paraneoplastic choreiform movements (along with other neurologic symptoms) are frequently associated with CV2/CRMP5 antibodies. In one comparison of clinical syndromes in patients with CV2/CRMP5 versus Hu antibodies, cerebellar ataxia and chorea was significantly more frequent in patients with CV2/CRMP5 antibodies [14••]. As with other paraneoplastic antibodies, CV2/CRMP5 antibodies are not specific for chorea and are found in NPSs, affecting the central as well as the peripheral nervous systems. Although CV2/CRMP5 antibodies and choreic movements occur more frequently with SCLC, they also have been reported in thymoma, lymphoma, and testicular cancer [36–38]. A patient with ballistic-choreiform movements as a presenting feature of renal cell carcinoma has been reported; he was negative for Hu antibodies, but whether he was tested for CV2/CRMP5 antibodies is not known [39]. Chorea as a feature of paraneoplastic anti-Yo and anti-Hu syndromes also has been reported [34,40]. With few exceptions, most patients with paraneoplastic chorea show basal ganglia abnormalities on MRI [41]. Differential diagnosis of paraneoplastic chorea is shown in Table 3.

Pharmacologic treatment with antihyperkinetics may provide symptomatic improvement in some cases. The mainstay of therapy is early detection and treatment of the underlying malignancy. In the study comparing patients with CV2/CRMP5 and Hu antibodies, the median survival time was significantly longer in patients with CV2/CRMP5 antibodies, and this effect was not dependent on the type of tumor [14••]. Of the 16 patients with paraneoplastic chorea described by Vernino et al. [33], four improved with chemotherapy for the underlying cancer and two improved with intravenous methylprednisolone.

Paraneoplastic Parkinsonism

Few cases of paraneoplastic parkinsonism have been reported. The probable pathophysiology involves immune-mediated destruction of the substantia nigra causing the parkinsonism. Golbe et al. [42] reported on a patient with metastatic carcinoma of the breast who rapidly developed parkinsonian signs and symptoms along with dystonia. The patient did not receive any benefit from the typical medications for Parkinson's disease (ie, levodopa, anticholinergics) and ultimately succumbed despite chemotherapy [42]. Another patient with more widespread multisystem affliction from breast cancer causing cerebellar degeneration, myopathy, parkinsonism (coarse upper extremity tremor), and cardiomyopathy responded well to block dissection of the carcinoma; her muscle weak-

ness was alleviated and her electrocardiogram returned to normal [43]. Fahn et al. [44] have also reported a case of rapidly progressive parkinsonism with incontinence, impotency, and levodopa-induced moaning in a patient with multiple myeloma. The patient was deemed to have levodopa-responsive parkinsonism from nigral degeneration attributable to a paraneoplastic etiology.

There are only two reported cases of paraneoplastic progressive supranuclear palsy in the literature. One case was in a 75-year-old man with vertical supranuclear palsy and postural instability with a fall within 1 year of onset. Some atypical features of supranuclear palsy that prompted the investigators to look for a secondary cause included spiking fevers, rapid progression of symptoms, and abnormal CSF findings; further workup led to the discovery of a large B-cell lymphoma [45]. The second case occurred in a 59-year-old woman with rapidly progressive supranuclear palsy secondary to bronchial adenocarcinoma [46]. She died 2 years after onset of her neurologic symptoms.

The rapid progression of the parkinsonism along with other atypical features that made the investigators suspicious of a secondary cause is an important commonality among all of the case reports described in this section.

Paraneoplastic sensory neuropathy sometimes may lead to dystonic movements that may result from loss of proprioception; this process has been termed *pseudoathetosis* (personal observation).

Paraneoplastic Tremors

This section addresses types of tremors that have a paraneoplastic etiology; patients with additional features who would meet the diagnosis of parkinsonism were discussed in the previous section. Valentino et al. [47] recently reported on a 58-year-old man with orolingual tremor secondary to anti-Hu paraneoplastic syndrome from non-SCLC. The EMG showed rhythmic activity (10-Hz frequency) from the orbicularis oris and levator labii superioris muscles. Treatment with clonazepam markedly decreased the tremor. Two patients reported by Phuphanich and Brock [10] with PCD and anti-Yo antibodies had tremor in addition to their cerebellar symptoms; we discussed them in the section on paraneoplastic ataxia. Several other groups have made similar observations of tremor in association with cerebellar symptoms in PCD [14••].

Paraneoplastic tremor has been reported as the sole presenting feature of SCLC with anti-Hu antibodies. A 55-year-old woman had a disabling tremor of 3- to 5-Hz frequency with standing or walking, and it resolved on lying down. The tremor affected her arms, legs, and head. With the initiation of chemotherapy, the tremor was markedly improved and she was able to stand and walk again [48].

Paraneoplastic Holmes' (rubral) tremor has been reported in a woman with advanced ovarian cancer with PCD, but no anti-Yo antibodies were found. The patient did not respond to clonazepam, levodopa, or immunoglobulins [49].

Paraneoplastic Anti-NMDA Receptor Encephalitis

Recently, a syndrome of psychiatric disturbances followed by complex movement disorders like stereotypy and dyskinesias with altered sensorium was described in women with ovarian tumors. This severe form of encephalitis is associated with antibodies against NR1 and NR2 heteromers of the *N*-methyl-D-aspartate (NMDA) receptor [50••]. In a case series of 100 patients with encephalitis and NR1/NR2 antibodies, 58 of 98 patients (59%) for whom oncological test results were available had tumors, most commonly ovarian teratomas [50••]. (Removal and/or treatment of the tumor and immunotherapy often results in stabilization or improvement in the clinical features.) Seventy-five of the 100 patients recovered or had mild deficits, and improvement was associated with a decrease in the serum antibody titers.

We had a similar experience with successful treatment of two patients with this syndrome (personal observations).

Rarely, a similar syndrome occurs in men with testicular teratoma. Eker et al. [51] reported on a patient with a testicular teratoma and seminoma who developed treatment-responsive encephalitis associated with antibodies to the NMDA receptor. After the tumor was treated aggressively with chemotherapy and surgery, the patient made a dramatic recovery. Interestingly, this case had clinical features similar to paraneoplastic anti-NMDA receptor encephalitis associated with ovarian teratoma, including occurrence at a young age, seizures, and cognitive and psychiatric symptoms accompanied by sequential development of predictable neurologic progression, including distinctive signs of extrapyramidal involvement.

Conclusions

Paraneoplastic movement disorders similar to NPSs occur in myriad malignancies and are associated with a host of paraneoplastic antibodies. Because the neurologic symptoms may manifest months before the cancer becomes overt, it is the neurologist who may bear the responsibility of diagnosing a paraneoplastic syndrome. A high index of suspicion, the presence of atypical features for common clinical diagnoses (eg, rapidly progressing parkinsonism), and a recognizable constellation of signs and symptoms for a paraneoplastic syndrome are essential to make an early diagnosis. Time is of the essence in such situations because an early diagnosis may prompt an intensive workup to detect an underlying cancer, which, if detected and treated early, may improve the final outcome and prognosis for the patient. Treatment of the underlying malignancy is essential to resolution of the paraneoplastic symptoms. Because these symptoms are immune mediated, suppression of the immune system may play a crucial role in the treatment of paraneoplastic neurologic symptoms.

Disclosure

No potential conflicts of interest relevant to this article were reported.

References and Recommended Reading

Papers of particular interest, published recently, have been highlighted as:

- • Of importance
- •• Of major importance

1. Poser JB: **Paraneoplastic syndromes.** *Rev Neurol (Paris)* 2002, **158:**899–906.
2. Darnell RB, Posner JB: **Paraneoplastic syndromes involving the nervous system.** *N Engl J Med* 2003, **349:**1543–1554.
3. Honnorat J, Antoine JC: **Paraneoplastic neurological syndromes.** *Orphanet J Rare Dis* 2007, **2:**22.
4. Drlicek M, Bianchi G, Bogliun G, et al.: **Antibodies of the anti-Yo and anti-Ri type in the absence of paraneoplastic neurological syndromes: a long-term survey of ovarian cancer patients.** *J Neurol* 1997, **244:**85–89.
5. Graus F, Delattre JY, Antoine JC, et al.: **Recommended diagnostic criteria for paraneoplastic neurological syndromes.** *J Neurol Neurosurg Psychiatry* 2004, **75:**1135–1140.
6. Dalmau J, Gonzalez RG, Lerwill MF: **Case records of the Massachusetts General Hospital. Case 4-2007. A 56-year-old woman with rapidly progressive vertigo and ataxia.** *N Engl J Med* 2007, **356:**612–620.
7. • Dalmau J, Rosenfeld MR: **Paraneoplastic syndromes of the CNS.** *Lancet Neurol* 2008, **7:**327–340.

This well-written review discusses paraneoplastic syndromes affecting the nervous system.

8. Aye MM, Kasai T, Tashiro Y, et al.: **CD8 positive T-cell infiltration in the dentate nucleus of paraneoplastic cerebellar degeneration.** *J Neuroimmunol* 2009, **208:**136–140.
9. Toothaker TB, Rubin M: **Paraneoplastic neurological syndromes: a review.** *Neurologist* 2009, **15:**21–33.
10. Phuphanich S, Brock C: **Neurologic improvement after high-dose intravenous immunoglobulin therapy in patients with paraneoplastic cerebellar degeneration associated with anti-Purkinje cell antibody.** *J Neurooncol* 2007, **81:**67–69.
11. Widdess-Walsh P, Tavee JO, Schuele S, Stevens GH: **Response to intravenous immunoglobulin in anti-Yo associated paraneoplastic cerebellar degeneration: case report and review of the literature.** *J Neurooncol* 2003, **63:**187–190.
12. Bernal F, Shams'ili S, Rojas I, et al.: **Anti-Tr antibodies as markers of paraneoplastic cerebellar degeneration and Hodgkin's disease.** *Neurology* 2003, **60:**230–234.
13. Shams'ili S, Grefkens J, de Leeuw B, et al.: **Paraneoplastic cerebellar degeneration associated with antineuronal antibodies: analysis of 50 patients.** *Brain* 2003, **126(Pt 6):**1409–1418.
14. •• Honnorat J, Cartalat-Carel S, Ricard D, et al.: **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* 2009, **80:**412–416.

The authors provide an elegant comparison of clinical features and outcomes of patients with anti-Hu antibodies and anti-CV2/CRMP5 antibodies showing that these antibodies are associated with specific neurologic symptoms and are not only markers of immune reaction.

15. Esposito M, Penza P, Orefice G, et al.: **Successful treatment of paraneoplastic cerebellar degeneration with rituximab.** *J Neurooncol* 2008, **86:**363–364.
16. Kraemer M, Berlit P: **Progressive encephalomyelitis with rigidity and myoclonus in an 81-year-old patient.** *Clin Neurol Neurosurg* 2008, **110:**279–281.
17. De Camilli P, Thomas A, Cofiell R, et al.: **The synaptic vesicle-associated protein amphiphysin is the 128-kD autoantigen of stiff-man syndrome with breast cancer.** *J Exp Med* 1993, **178:**2219–2223.
18. • Murinson BB, Guarnaccia JB: **Stiff-person syndrome with amphiphysin antibodies: distinctive features of a rare disease.** *Neurology* 2008, **71:**1955–1958.

The authors provide a good discussion and case series of paraneoplastic SPS associated with amphiphysin antibodies.

19. Nguyen-Huu BK, Urban PP, Schreckenberger M, et al.: **Anti-amphiphysin-positive stiff-person syndrome associated with small cell lung cancer.** *Mov Disord* 2006, **21:**1285–1287.
20. McHugh JC, Murray B, Renganathan R, et al.: **GAD antibody positive paraneoplastic stiff person syndrome in a patient with renal cell carcinoma.** *Mov Disord* 2007, **22:**1343–1346.
21. McCabe DJ, Turner NC, Chao D, et al.: **Paraneoplastic "stiff person syndrome" with metastatic adenocarcinoma and anti-Ri antibodies.** *Neurology* 2004, **62:**1402–1404.
22. Butler MH, Hayashi A, Ohkoshi N, et al.: **Autoimmunity to gephyrin in stiff-man syndrome.** *Neuron* 2000, **26:**307–312.
23. Tate ED, Allison TJ, Pranzatelli MR, Verhulst SJ: **Neuroepidemiologic trends in 105 US cases of pediatric opsoclonus-myoclonus syndrome.** *J Pediatr Oncol Nurs* 2005, **22:**8–19.
24. Kirsten A, Beck S, Fühlhuber V, et al.: **New autoantibodies in pediatric opsoclonus myoclonus syndrome.** *Ann N Y Acad Sci* 2007, **1110:**256–260.
25. • Wong A: **An update on opsoclonus.** *Curr Opin Neurol* 2007, **20:**25–31.

The author provides an interesting update on opsoclonus with an emphasis on immune mechanisms and pathophysiology of the disorder.

26. Kumar A, Lajara-Nanson WA, Neilson RW Jr: **Paraneoplastic opsoclonus-myoclonus syndrome: initial presentation of non-Hodgkins lymphoma.** *J Neurooncol* 2005, **73:**43–45.
27. Bataller L, Graus F, Saiz A, et al.: **Clinical outcome in adult onset idiopathic or paraneoplastic opsoclonus-myoclonus.** *Brain* 2001, **124:**437–443.
28. Gabaldon-Torres L, Fernandez-Dominguez J, Salas-Felipe J, et al.: **Opsoclonus-myoclonus-ataxia syndrome: two anatomoclinical case reports.** *Rev Neurol* 2009, **48:**137–140.
29. Fitzpatrick AS, Gray OM, McConville J, McDonnell GV: **Opsoclonus-myoclonus syndrome associated with benign ovarian teratoma.** *Neurology* 2008, **70:**1292–1293.
30. Jung KY, Youn J, Chung CS: **Opsoclonus-myoclonus syndrome in an adult with malignant melanoma.** *J Neurol* 2006, **253:**942–943.
31. Van Diest D, De Raeve H, Claes J, et al.: **Paraneoplastic opsoclonus-myoclonus-ataxia (OMA) syndrome in an adult patient with esthesioneuroblastoma.** *J Neurol* 2008, **255:**594–596.
32. Straube A, Leigh RJ, Bronstein A, et al.: **EFNS task force--therapy of nystagmus and oscillopsia.** *Eur J Neurol* 2004, **11:**83–89.
33. Vernino S, Tuite P, Adler CH, et al.: **Paraneoplastic chorea associated with CRMP-5 neuronal antibody and lung carcinoma.** *Ann Neurol* 2002, **51:**625–630.
34. Krolak-Salmon P, Androdias G, Meyronet D, et al.: **Slow evolution of cerebellar degeneration and chorea in a man with anti-Yo antibodies.** *Eur J Neurol* 2006, **13:**307–308.
35. Kinirons P, Fulton A, Keoghan M, et al.: **Paraneoplastic limbic encephalitis (PLE) and chorea associated with CRMP-5 neuronal antibody.** *Neurology* 2003, **61:**1623–1624.
36. Yu Z, Kryzer TJ, Griesmann GE, et al.: **CRMP-5 neuronal autoantibody: marker of lung cancer and thymoma-related autoimmunity.** *Ann Neurol* 2001, **49:**146–154.
37. Nuti A, Ceravolo R, Salvetti S, et al.: **Paraneoplastic choreic syndrome during non-Hodgkin's lymphoma.** *Mov Disord* 2000, **15:**350–352.
38. Kellinghaus C, Kraus J, Blaes F, et al.: **CRMP-5-autoantibodies in testicular cancer associated with limbic encephalitis and choreiform dyskinesias.** *Eur Neurol* 2007, **57:**241–243.

39. Kujawa KA, Niemi VR, Tomasi MA, et al.: **Ballistic-choreic movements as the presenting feature of renal cancer.** *Arch Neurol* 2001, **58:**1133–1135.
40. Dorban S, Gille M, Kessler R, et al.: **Chorea-athetosis in the anti-Hu syndrome.** *Rev Neurol (Paris)* 2004, **160:**126–129.
41. Tremont-Lukats IW, Fuller GN, Ribalta T, et al.: **Paraneoplastic chorea: case study with autopsy confirmation.** *Neuro Oncol* 2002, **4:**192–195.
42. Golbe LI, Miller DC, Duvoisin RC: **Paraneoplastic degeneration of the substantia nigra with dystonia and parkinsonism.** *Mov Disord* 1989, **4:**147–152.
43. Mousa AR, Al-Din AN: **Neurological and cardiac complications of carcinoma of the breast. Case report.** *Acta Neurol Scand* 1985, **72:**518–521.
44. Fahn S, Brin MF, Dwork AJ, et al.: **Case 1, 1996: rapidly progressive parkinsonism, incontinence, impotency, and levodopa-induced moaning in a patient with multiple myeloma.** *Mov Disord* 1996, **11:**298–310.
45. 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:**187–191.
46. Jankovic J: **Progressive supranuclear palsy: paraneoplastic effect of bronchial carcinoma.** *Neurology* 1985, **35:**446–447.
47. Valentino P, Labate A, Pirritano D, et al.: **Orolingual tremor as unusual presentation of anti-Hu paraneoplastic syndrome.** *Mov Disord* 2008, **23:**1791–1792.
48. Gilhuis HJ, van Ommen HJ, Pannekoek BJ, et al.: **Paraneoplastic orthostatic tremor associated with small cell lung cancer.** *Eur Neurol* 2005, **54:**225–226.
49. Simonetti F, Pergami P, Aktipi KM, et al.: **Paraneoplastic "rubral" tremor: a case report.** *Mov Disord* 1998, **13:**612–614.
50.•• Dalmau J, Gleichman AJ, Hughes EG, et al.: **Anti-NMDA-receptor encephalitis: case series and analysis of the effects of antibodies.** *Lancet Neurol* 2008, **7:**1091–1098.
The authors present an excellent discussion of a new paraneoplastic disorder, outlining the distinctive clinical features and immunopathogenesis responsible for the syndrome.
51. Eker A, Saka E, Dalmau J, et al.: **Testicular teratoma and anti-N-methyl-D-aspartate receptor-associated encephalitis.** *J Neurol Neurosurg Psychiatry* 2008, **79:**1082–1083.