

Managing Paraneoplastic Neurological Disorders

JANET W. DE BEUKELAAR, PETER A. SILLEVIS SMITT

Erasmus University Medical Center, Rotterdam, The Netherlands

Key Words. Paraneoplastic neurological syndromes • Cancer • Autoimmunity • Autoantibodies • Onconeural antigens

LEARNING OBJECTIVES

After completing this course, the reader will be able to:

1. Describe the autoimmune pathogenesis of paraneoplastic neurological syndromes.
2. Explain the clinical value of paraneoplastic antibody detection.
3. Describe the general treatment approach to paraneoplastic neurological syndromes.

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ABSTRACT

Paraneoplastic neurological syndromes (PNS) are remote effects of cancer that are not caused by invasion of the tumor or its metastases. Immunologic factors appear important in the pathogenesis of PNS because antineuronal autoantibodies and T-cell responses against nervous system antigens have been defined for many of these disorders. The immunologic response is elicited by the ectopic expression of neuronal antigens by the tumor. Expression of these so-called “onconeural” antigens is limited to the tumor and the nervous system and sometimes also the testis. At the time of presentation of the neurological symptoms, most patients have not yet been diagnosed with cancer. Detection of paraneoplastic antibodies is extremely helpful in diagnosing an otherwise unexplained and often rapidly progressive neurological syndrome as paraneoplastic. In addition,

the paraneoplastic antibodies may also direct the search for an underlying neoplasm. On the other hand, in patients known to have cancer, the presentation of a PNS may herald recurrence of the tumor or a second tumor. The number of paraneoplastic antibodies is still growing, and at least seven of these can now be considered well characterized. Based on the clinical syndrome, the type of antibody, and the presence or absence of cancer, patients are classified as having a “definite” or “possible” PNS. Despite the presumed autoimmune etiology of PNS, the results of various forms of immunotherapy have been disappointing, with some exceptions. Rapid detection and immediate treatment of the underlying tumor appears to offer the best chance of stabilizing the patient and preventing further neurological deterioration. *The Oncologist* 2006;11:292–305

INTRODUCTION

Paraneoplastic neurological syndromes (PNS) are remote effects of cancer that are, by definition, caused neither by invasion of the tumor or its metastases nor by infection, ischemia, metabolic and nutritional deficits, surgery, or

other forms of tumor treatment [1]. Immunologic factors are believed to be important in the pathogenesis of PNS because antibodies and T-cell responses against nervous system antigens have been defined for many of these disorders [1]. Presumably, the immunologic response is elicited

Correspondence: Peter Sillevius Smitt, M.D., Ph.D., Department of Neurology, Room H664, Erasmus University Medical Center, Dr Molewater 40, 3015 GD, Rotterdam, The Netherlands. Telephone: 00-31-10-4633327; Fax: 00-31-10-4632156; e-mail: p.sillevismitt@erasmusmc.nl Received August 9, 2005; accepted for publication January 2, 2006. ©AlphaMed Press 1083-7159/2006/\$20.00/0

by the ectopic expression of neuronal antigens by the tumor. Expression of these “onconeural” antigens is limited to the tumor and the nervous system, and sometimes also the testis. At the time of presentation of the neurological symptoms, most patients have not yet been diagnosed with cancer [2–5]. Detection of paraneoplastic antibodies can help diagnose the neurological syndrome as paraneoplastic and may direct the search for an underlying neoplasm. Often, the oncologist or hematologist will be involved in the tumor workup. On the other hand, in patients known to have cancer, the presentation of a PNS may herald recurrence of the tumor or a second tumor. In these patients, however, metastatic complications of the known cancer must be ruled out first. Despite the presumed autoimmune etiology of PNS, the results of various forms of immunotherapy have been disappointing, with some exceptions [2–5]. Rapid detection and immediate treatment of the underlying tumor appears to offer the best chance of stabilizing the patient and preventing further neurological deterioration [2–5].

PATHOGENESIS

Pathological examination of the nervous system generally shows loss of neurons in affected areas of the nervous system with inflammatory infiltration by CD4⁺ T-helper cells and B cells in the perivascular spaces and cytotoxic CD8⁺ T cells in the interstitial spaces [6–8]. Examination of the cerebrospinal fluid (CSF) frequently demonstrates pleocytosis, intrathecal synthesis of IgG, and oligoclonal bands, supporting an inflammatory or immune-mediated etiology.

The discovery of paraneoplastic antineuronal autoantibodies resulted in the general belief that these are immune-mediated disorders triggered by aberrant expression of onconeural antigens in the tumor. Support for this hypothesis comes from the fact that the target paraneoplastic antigens are expressed both in the tumor and in the affected parts of the nervous system. Furthermore, the tumors are usually small and heavily infiltrated with inflammatory cells, and spontaneous remissions at the time of neurological presentation have been described [9, 10]. These findings suggest that some PNS without an identifiable tumor may result from immune-mediated eradication of the tumor [9, 10]. In keeping with this hypothesis, one study found more limited disease distribution and better oncologic outcome in small cell lung cancer (SCLC) patients with paraneoplastic autoantibodies [11].

Although the paraneoplastic antibodies are synthesized intrathecally, a pathogenic role could only be proven for those paraneoplastic autoantibodies that are directed against easily accessible antigens located at the cell surface. Examples of such antigens are the acetylcholine receptor (anti-AChR muscle type in myasthenia gravis

and neuronal ganglionic type in autonomic neuropathy), P/Q-type voltage-gated calcium channels (anti-VGCC in Lambert-Eaton myasthenic syndrome [LEMS]), voltage-gated potassium channels (anti-VGKC in neuromyotonia), and the metabotropic glutamate receptor mGluR1 (anti-mGluR1 in paraneoplastic cerebellar degeneration [PCD]). Most paraneoplastic antigens are located in the cytoplasm (e.g., the Yo antigen) or nucleus (e.g., the Hu and Ri antigens), and a pathogenic role for the respective antibodies has not been demonstrated [12]. In these disorders, indirect lines of evidence support the view that the cellular immune response against these antigens is responsible for the neurological damage [13–15]. The relative contribution of the cellular and humoral immunity to the clinical and pathological manifestations has not been resolved [13–15]. The paraneoplastic antibodies may, in these cases, be surrogate markers for T-lymphocyte activation [16].

A totally different mechanism seems at work in PCD in Hodgkin's lymphoma because the target antigens of the associated anti-Tr and anti-mGluR1 autoantibodies are not expressed in Hodgkin's tumor tissue [17]. Dysregulation of the immune system in Hodgkin's lymphoma and an etiologic role for (viral?) infections have been postulated in this disorder.

INCIDENCE

The incidence of PNS varies with the neurological syndrome and with the tumor. Approximately 10% of patients with plasma cell disorders accompanied by malignant monoclonal gammopathies are affected by a paraneoplastic peripheral neuropathy. More than half of the patients with the rare osteosclerotic form of myeloma develop a severe predominantly motor paraneoplastic peripheral neuropathy. In other hematological malignancies, the incidence of PNS is very low, with the exception of Hodgkin's disease. However, the incidence of PNS even in Hodgkin's disease is well below 1%. In solid tumors, the more common neurological syndromes are myasthenia gravis, which occurs in 15% of patients with a thymoma, and LEMS, which affects 3% of patients with SCLC. For other solid tumors, the incidence of PNS is <1%.

DIAGNOSIS

Clinical syndromes are never pathognomonic for a paraneoplastic etiology, and a high index of clinical suspicion is important. Symptoms can be atypical, psychiatric, or even fluctuating, and PNS should often be in the differential diagnosis of otherwise unexplained neurological syndromes. Some neurological syndromes, such as limbic encephalitis and subacute cerebellar degeneration, are associated relatively often with cancer. These are called

“classical” PNS and are in italics in Table 1 [18]. Other syndromes, such as sensorimotor polyneuropathy, are much more prevalent, and their association with cancer may be by chance. Detection of a “well-characterized” paraneoplastic antibody is extremely helpful because it proves the paraneoplastic etiology of the neurological syndrome. The paraneoplastic antibodies are generally divided into three categories (Table 2) [18]. The well-characterized antibodies are reactive with molecularly defined onconeural antigens. These antibodies are strongly associated with cancer and have been detected unambiguously by several laboratories in a reasonable number of patients with well-defined neurological syndromes [18]. The partially characterized antibodies are those with an unidentified target antigen and those that have either been described by a single group of investigators or have been reported in only a few patients. The third group consists of antibodies that are associated with specific disorders but do not differentiate between paraneoplastic and nonparaneoplastic cases.

Because different antibodies can be associated with the same clinical findings [4], and the same antibody can be associated with different clinical syndromes [2,

3], paraneoplastic antibodies should be searched for by screening rather than by focusing on a specific antibody. Recently, Pittock et al. [19] demonstrated, in a large prospective series, that approximately 30% of patients have more than one paraneoplastic antibody. The combination of paraneoplastic antibodies provides important additional information to narrow the search for an underlying malignancy [19].

In the absence of paraneoplastic antibodies, additional diagnostic tests may be helpful in some PNS, although these are never specific for a paraneoplastic etiology. Magnetic resonance imaging (MRI) can help diagnose limbic encephalitis and may demonstrate cerebellar atrophy several months after the onset of PCD. Examination of the CSF is generally not required for detection of paraneoplastic antibodies because these can almost always be detected in serum as well. CSF examination may, however, show signs of inflammation, such as elevated white cell counts, oligoclonal bands, and intrathecal synthesis of IgG, indicating an immune-mediated or inflammatory etiology. In patients known to have cancer, MRI and CSF cytology are important in ruling out leptomeningeal metastases. Some PNS of the peripheral nervous system, such as LEMS, myasthenia gravis, and neuromyotonia, are accompanied by characteristic electrophysiological changes. These findings, however, are also present in the absence of an underlying tumor. Determining the precise type of neurological syndrome may assist in the search for an underlying tumor, such as SCLC in LEMS and thymoma in myasthenia gravis.

Once a paraneoplastic diagnosis has been established or is suspected, rapid identification of the tumor becomes essential but may be difficult because most PNS develop in the early stages of cancer. The workup generally starts with a detailed history, including smoking habits, weight loss, night sweats, and fever. A thorough physical examination should include palpation for pathological lymph nodes, rectal and pelvic examination, and palpation of breasts and testis. Often, the tumor is detected by high-resolution computed tomography (CT) of the chest, abdomen, and pelvis. If the CT scan remains negative, whole-body fluorodeoxyglucose positron emission tomography (FDG-PET) or PET/CT is recommended to detect an occult tumor or its metastases [20–22]. In addition, the type of antibody and PNS may suggest a specific underlying tumor and indicate further diagnostic tests, such as mammography (may be replaced by MRI) or ultrasound of the testes or pelvis (Table 2). When all tests remain negative, repeat evaluation at 3- to 6-month intervals for 2–3 years is recommended.

Diagnosing a neurological syndrome as paraneoplastic requires the exclusion of other possible causes by a

Table 1. Paraneoplastic neurological syndromes

Central nervous system
<i>Encephalomyelitis</i>
<i>Limbic encephalitis</i>
Brainstem encephalitis
<i>Subacute cerebellar degeneration</i>
<i>Opsoclonus-myoclonus</i>
Stiff-person syndrome
Paraneoplastic visual syndromes
Cancer-associated retinopathy
Melanoma-associated retinopathy
Paraneoplastic optic neuropathy
Motor neuron syndromes
Subacute motor neuronopathy
Other motor neuron syndromes
Peripheral nervous system
<i>Subacute sensory neuronopathy</i>
Acute sensorimotor neuropath
Chronic sensorimotor neuropathy
Association with M-proteins
Subacute autonomic neuropathy
Paraneoplastic peripheral nerve vasculitis
Neuromuscular junction and muscle
<i>Lambert-Eaton myasthenic syndrome</i>
Myasthenia gravis
Neuromyotonia
<i>Dermatomyositis</i>
Acute necrotizing myopathy
Cachectic myopathy

Classical paraneoplastic neurological syndromes are in italics.

Table 2. Antibodies, paraneoplastic neurological syndromes, and associated tumors

Antibody	Clinical syndromes	Associated tumors
Well-characterized paraneoplastic antibodies		
Anti-Hu (ANNA-1)	Encephalomyelitis, limbic encephalitis, sensory neuronopathy, subacute cerebellar degeneration, autonomic neuropathy	SCLC, neuroblastoma, prostate
Anti-Yo (PCA-1)	Subacute cerebellar degeneration	Ovary, breast
Anti-CV2 (CRMP5)	Encephalomyelitis, chorea, limbic encephalitis, sensory neuronopathy, sensorimotor neuropathy, optic neuritis, subacute cerebellar degeneration, autonomic neuropathy	SCLC Thymoma
Anti-Ri (ANNA-2)	Opsoclonus-myoclonus, brainstem encephalitis	Breast, SCLC
Anti-Ma2 (Ta) ^a	Limbic/diencephalic/brainstem encephalitis, subacute cerebellar degeneration	Testicle, lung
Anti-amphiphysin	Stiff-person syndrome, encephalomyelitis, subacute sensory neuronopathy, sensorimotor neuropathy	Breast, SCLC
Anti-recoverin	Cancer-associated retinopathy	SCLC
Partially characterized antibodies		
Anti-Tr (PCA-Tr)	Subacute cerebellar degeneration	Hodgkin's disease
ANNA-3	Encephalomyelitis, subacute sensory neuronopathy	SCLC
PCA-2	Encephalomyelitis, subacute cerebellar degeneration	SCLC
Anti-Zic4	Subacute cerebellar degeneration	SCLC
Anti-mGluR1	Subacute cerebellar degeneration	Hodgkin's disease
Antibodies that occur with and without cancer		
Anti-VGCC	Lambert-Eaton myasthenic syndrome, subacute cerebellar degeneration	SCLC
Anti-AchR	Myasthenia gravis	Thymoma
Anti-nAChR	Subacute autonomic neuropathy	SCLC
Anti-VGKC	Limbic encephalitis, neuromyotonia	Thymoma, SCLC

^aBrainstem encephalitis and subacute cerebellar degeneration are usually associated with tumors other than testicular cancer and sera from these patients also react with the Ma1 protein.

Abbreviations: AChR, acetylcholine receptor; ANNA, antineuronal nuclear antibody; mGluR1, metabotropic glutamate receptor type 1; nAChR, nicotinic acetylcholine receptor; PCA, Purkinje cytoplasmic antibody; SCLC, small cell lung carcinoma; VGCC, voltage-gated calcium channels; VGKC, voltage-gated potassium channel.

reasonably complete workup. Because of the difficulties in diagnosis, an international panel of neurologists has established diagnostic criteria that divide patients with a suspected PNS into “definite” and “probable” categories. These criteria are based on the presence or absence of cancer, the presence of well-characterized antibodies, and the type of clinical syndrome. Patients with a definite PNS include those with [18]:

(a) A classical syndrome (i.e., encephalomyelitis, limbic encephalitis, subacute cerebellar degeneration, opsoclonus-myoclonus, subacute sensory neuronopathy, chronic gastrointestinal pseudo-obstruction, LEMS, or dermatomyositis) and cancer that develops within 5 years of the diagnosis of the neurological disorder, regardless of the presence of paraneoplastic antibodies.

(b) A nonclassical syndrome that objectively improves or resolves after cancer treatment, provided that the syndrome is not susceptible to spontaneous remission.

(c) A nonclassical syndrome with paraneoplastic antibodies (well characterized or not) and cancer that develops within 5 years of the diagnosis of the neurological disorder.

(d) A neurological syndrome (classical or not) with well-characterized paraneoplastic antibodies (i.e., anti-Hu, anti-Yo, anti-Ri, anti-amphiphysin, anti-CV2, or anti-Ma2).

Patients with a possible PNS include those with [18]:

(a) A classical syndrome without paraneoplastic antibodies and no cancer but at high risk to have an underlying tumor (e.g., smoking habit).

(b) A neurological syndrome (classical or not) without cancer but with partially characterized paraneoplastic antibodies.

(c) A nonclassical neurological syndrome, no paraneoplastic antibodies, and cancer that presents within 2 years of the neurological syndrome.

TREATMENT AND PROGNOSIS

Despite the immunological etiology of most of the PNS, the results of immunotherapy have been disappointing [23]. Exceptions are the neurological syndromes associated with paraneoplastic antibodies that are directed against antigens that are located at the surface of the cell (i.e., antigens that are accessible to circulating antibodies). These include not only disorders of the peripheral nervous system (LEMS, myasthenia gravis, and neuromyotonia) but also anti-mGluR1-associated PCD and anti-amphiphysin-associated stiff-person syndrome [24, 25]. Immunotherapy modalities that are recommended for these disorders include plasma exchange, immunoadsorption (extraction of patient IgG over a protein A column), steroids, and i.v. Ig.

For most PNS, when the antigen is cytoplasmic or nuclear, the nervous dysfunction is probably not caused by functional interference of antibodies with the target antigen. In disorders with intracellular target antigens and a strong cellular immune reaction, plasma exchange and immunoadsorption are not expected to give much benefit. In these cases, a trial of a treatment that modulates the activation and function of effector T cells makes more sense, but to date there is only limited evidence that steroids, cyclophosphamide, i.v. Ig, or other immunosuppressive therapies are effective [26].

Hence, the first goal of treatment for PNS is control of the tumor. In addition, antitumor therapy has been demonstrated to stop the paraneoplastic neurological deterioration and leave the patients, on average, in better condition [27]. In severely debilitated patients, for example, the elderly and bedridden, treatment of the underlying tumor is often withheld because of the very small chance of clinically relevant neurological improvement.

Table 3 provides a summary of treatment of PNS and the effect on neurological outcome.

CLINICAL SYNDROMES

The classical PNS are described below. Descriptions of the nonclassical syndromes, which usually are not paraneoplastic but may occur in association with cancer, can be found elsewhere [28].

Encephalomyelitis

Paraneoplastic encephalomyelitis is characterized by involvement of several areas of the nervous system, including the temporal lobes and limbic system (limbic encephalitis), brainstem (brainstem encephalitis), cerebellum (subacute cerebellar degeneration), spinal cord (myelitis) dorsal root ganglia (subacute sensory neuronopathy), and autonomous nervous system (autonomic neuropathy) [29, 30]. Patients with predominant involvement of one area but

clinical evidence of only mild involvement of other areas are usually classified according to the predominant clinical syndrome. Symptoms of limbic encephalitis, subacute cerebellar degeneration, subacute sensory neuronopathy, and autonomic neuropathy are described below. Symptoms of brainstem encephalitis can include diplopia, dysarthria, dysphagia, gaze abnormalities (nuclear, internuclear, or supranuclear), facial numbness, and subacute hearing loss.

Underlying Tumor

Although virtually all cancer types have been associated with paraneoplastic encephalomyelitis, the majority of patients have underlying SCLC [2, 3, 29–31]. Most patients are not known to have cancer when the neurological symptoms present, and the SCLC may be difficult to demonstrate because of its small size. When anti-Hu antibodies are detected or when the patient is at risk for lung cancer (smoking, age >50 years), a careful and repeated search for underlying SCLC is warranted. When the CT scan is negative, a total-body FDG-PET scan or FDG-PET/CT scan may detect the neoplasm [20, 21]. When a tumor other than SCLC is detected in a patient with anti-Hu antibodies, it may unexpectedly express the Hu antigen [2] or may be an unrelated secondary neoplasm [31]. When tumor tissue is available for analysis and expresses the Hu antigen, a further workup for a second tumor (SCLC) can probably be safely deferred [2].

Diagnostic Evaluation

MRI or CT of the brain is normal or shows specific changes in most paraneoplastic encephalomyelitis patients with two exceptions [30]. In 65%–80% of patients with predominant limbic encephalitis, MRI and CT show temporal lobe abnormalities [32, 33]. Patients with a predominant cerebellar syndrome will develop cerebellar atrophy in the chronic stage. CSF is abnormal in most patients, showing elevated protein, mild mononuclear pleocytosis, elevated IgG index, or oligoclonal bands [30].

Antineuronal Antibodies

Patients with paraneoplastic encephalomyelitis and SCLC often have anti-Hu antibodies (also called antineuronal nuclear autoantibodies [ANNA-1]) in their serum and CSF [2, 3, 30, 31]. Other antibodies associated with paraneoplastic encephalomyelitis include anti-CRMP5/CV2 [16], anti-amphiphysin [34], and the less well-characterized ANNA-3 [35] and Purkinje cell antibody, PCA-2 [36].

Treatment and Prognosis

Tumor treatment offers the best chance of stabilizing the patient's neurological condition, while immunotherapy does not appear to modify the outcome of paraneoplastic enceph-

Table 3. Paraneoplastic neurological syndromes and their response to treatment

Clinical syndrome	Autoantibody	Response to immunotherapy	Response to tumor therapy	Comments
Encephalomyelitis	Hu (ANNA-1)	No established effect	Stabilizes the patient in better condition	Spontaneous improvement very rarely described
Limbic encephalitis	Hu (ANNA-1), Ma2	Some patients respond	May improve	Partial improvement may occur spontaneously
Subacute cerebellar degeneration	Yo (PCA-1)	No established effect	No effect on neurological outcome	
	Tr (PCA-Tr), mGluR1	May improve	May improve	Subacute cerebellar degeneration associated with Hodgkin's disease may also improve spontaneously
Opsoclonus-myoclonus (adults)	Ri (ANNA-2)	May improve	Partial neurological recovery	Thiamin, baclofen, and clonazepam may be effective
Opsoclonus-myoclonus (pediatric)	No antibody	Two thirds improve	Partial neurological recovery	
Stiff-person syndrome	Amphiphysin	May improve	May improve	Responds to baclofen, diazepam, valproate, vigabatrin, and carbamazepine; painful spasms may require opioids
Cancer-associated retinopathy	Recoverin	Vision may slightly improve	No established effect	
Melanoma-associated retinopathy	Anti-bipolar cells	Anecdotal vision improvement	Anecdotal vision improvement	
Paraneoplastic optic neuropathy	CV2/CRMP5	Anecdotal vision improvement	Anecdotal vision improvement	
Subacute sensory neuronopathy	Hu (ANNA-1)	No established effect; rare partial responses	Stabilizes the patient in better condition	Treatment of neuropathic pain with tricyclic antidepressants and anti-epileptic drugs
Chronic sensorimotor neuropathy with M-protein	MAG (IgM)	May improve	May improve	
Chronic sensorimotor neuropathy with osteosclerotic myeloma	No antibody	No established effect	Often responds	Radiotherapy, chemotherapy, and surgery effective
Subacute autonomic neuropathy	Hu	No established effect	No established effect	Symptomatic treatment of orthostatic hypotension; neostigmine in pseudo-obstruction
Paraneoplastic peripheral nerve vasculitis	Hu	May improve	May improve	
Lambert-Eaton myasthenic syndrome	P/Q-type VGCC	Often responds	Often responds	2,3 diaminopyridine; cholinesterase inhibitors may be tried (efficacy unclear)
Myasthenia gravis	AChR	Often responds	Often responds	Cholinesterase inhibitors
Neuromyotonia	VGKC	May respond	Not known	Antiepileptic drugs (carbamazepine, phenytoin)
Dermatomyositis	Mi-2	Usually responds	May respond	

Abbreviations: AChR, acetylcholine receptor; ANNA, antineuronal nuclear antibody; MAG, myelin-associated glycoprotein; mGluR1, metabotropic glutamate receptor type 1; PCA, Purkinje cytoplasmic antibody; VGCC, voltage-gated calcium channels; VGKC, voltage-gated potassium channel.

alomyelitis [2, 3, 23]. Therefore, all efforts should be directed at early diagnosis of paraneoplastic encephalomyelitis and rapid identification and treatment of the tumor. Because of incidental reports of neurological improvement following various forms of immunosuppressive treatment, a trial of one or two immunosuppressive modalities may be warranted in a single patient. However, spontaneous neurological improve-

ment has rarely been described [10]. The overall functional outcome is bad, and more than 50% of patients are confined to bed or chair in the chronic phase of the disease [2, 3, 23]. The median survival time of patients is approximately 1 year from diagnosis [2, 3]. Mortality is predicted by worse functional status at diagnosis, age >60 years, involvement of more areas of the nervous system, and absence of treatment [2].

Because of the limited efficacy of plasma exchange, i.v. Ig, and corticosteroids [2, 3, 23] and the presumed role of cellular immunity, more aggressive immunosuppression with cyclophosphamide, tacrolimus, or cyclosporine may be considered. To limit toxicity, these more aggressive immunosuppressive approaches should probably be reserved for patients who are not receiving chemotherapy.

Limbic Encephalitis

Paraneoplastic limbic encephalitis (PLE) is a rare disorder characterized by the subacute onset (in days to a few months) of short-term memory loss, seizures, confusion, and psychiatric symptoms suggesting involvement of the limbic system [29, 37]. Hypothalamic dysfunction may occur with somnolence, hyperthermia, and endocrine abnormalities. Selective impairment of recent memory is a hallmark of the disease but may not be evident in patients presenting with severe confusion or multiple seizures [33]. More than half of the patients presenting with limbic encephalitis may have an underlying neoplasm [33]. Clinically three groups of patients with PLE can be identified [33]. The first group consists of patients with anti-Hu antibodies and lung cancer (usually SCLC). The limbic encephalitis is part of paraneoplastic encephalomyelitis, and the patients have involvement of other areas outside the limbic system and brainstem. These patients are older (median age, 62 years), usually smoke, and are more often female [33, 38]. The second group consists of young males with testicular cancer and anti-Ma2 antibodies [39]. The median age is 34 years. Symptoms are usually confined to the limbic system, hypothalamus, and brainstem. The third group has no antineuronal antibodies (approximately 40% of patients with PLE) [32, 33]. In these patients, the symptoms are more often confined to the limbic system, the median age is around 57 years, and the associated tumor is often located in the lung [33, 38].

Underlying Tumor

The associated tumor is a lung tumor in 50%–60% of patients, usually SCLC (40%–55%), and the associated tumor is a testicular germ cell tumor in 20% of patients [32, 33, 38]. Other tumors include breast cancer, thymoma, Hodgkin's disease, and immature teratomas [32, 33].

Diagnostic Evaluation

The diagnosis is often difficult because there are no specific clinical markers and symptoms usually precede the diagnosis of cancer [33]. MRI and CT scans are abnormal in 65%–80% of patients [32, 33]. Abnormalities consist of increased signal on T2-weighted and fluid-attenuated inversion-recovery images of one or both medial temporal

lobes, hypothalamus, and brainstem. Early in the course of the disease, the MRI scan may be normal, and repeat imaging may be indicated. Co-registration of FDG-PET may further improve the sensitivity of imaging [40]. CSF examination is abnormal in 80% of patients, showing transient mild lymphocytic pleocytosis with elevated protein, IgG, or oligoclonal bands [32, 33]. Detection of paraneoplastic antibodies helps establish the diagnosis and direct a tumor search that should include the lung, breasts, and testicles in the absence of paraneoplastic antibodies.

Antineuronal Antibodies

Antineuronal antibodies are found in about 60% of patients with PLE. The most frequent related paraneoplastic antibodies are: anti-Hu, anti-Ma2 (with or without Ma1), anti-CV2/CRMP5, and anti-amphiphysin [16, 33, 41]. The majority of patients with anti-Hu antibodies have symptoms that suggest dysfunction of areas of the nervous system outside the limbic system. The related tumor in these patients is usually SCLC. Patients with only anti-Ma2 antibodies (also called anti-Ta) are young males with testicular cancer. Patients with anti-Ma2 and anti-Ma1 antibodies are significantly older and are more often female [41]. Anti-Ma1 patients are more likely to develop cerebellar dysfunction and usually harbor tumors other than testicular cancer. Anti-CV2/CRMP5 antibodies are detected in patients with SCLC or thymoma [16]. Anti-VGKC antibodies can be associated with PLE and thymoma or with non-paraneoplastic limbic encephalitis [42, 43].

Treatment and Prognosis

Spontaneous complete recovery has been described, although very rarely [38, 44]. Immunotherapy is largely ineffective [33], but several cases benefiting from antitumor treatment have been reported [33, 38, 45]. Therefore, all efforts should be directed at identifying and treating the underlying tumor. If no tumor is found, the search should be repeated every 3–6 months for a total of 2–3 years. Irrespective of treatment, partial neurological recovery was seen in 38% of patients with anti-Hu antibodies, 30% of patients with anti-Ta (anti-Ma2) antibodies, and 64% of patients without antibodies [33].

Subacute Cerebellar Degeneration

PCD is one of the most common and characteristic PNS [4, 29]. In a study of 137 consecutive patients with antibody-associated PNS, 50 (37%) presented with subacute cerebellar degeneration [4]. PCD usually starts acutely with nausea, vomiting, dizziness, and slight incoordination of walking, evolving rapidly over weeks to a few months with progressive ataxia of gait, limbs, and trunk, dysarthria, and

often nystagmus associated with oscillopsia. The disease reaches its peak within months and then stabilizes. By this time, most patients are severely debilitated. They are generally unable to walk without support, they may be unable to sit unsupported, handwriting is often impossible, and feeding themselves has become difficult. The neurological signs are always bilateral but may be asymmetrical. Diplopia is common at presentation, although the investigator usually cannot detect abnormalities of ocular movement. The symptoms and signs are limited to the cerebellum and cerebellar pathways, but other mild neurological abnormalities may be found on careful examination. These include hearing loss, dysphagia, pyramidal and extrapyramidal tract signs, mental status change, and peripheral neuropathy [5, 46, 47].

Underlying Tumor

PCD can be associated with any cancer, but the most common tumors are lung cancer (usually SCLC), ovarian cancer, and lymphomas (particularly Hodgkin's lymphoma). In 60%–70% of patients, neurological symptoms precede diagnosis of the cancer by a few months to 2–3 years and lead to its detection [4, 5, 17].

Diagnostic Evaluation

Subacute cerebellar degeneration is a rare disorder in cancer patients. On the other hand, 50% of patients presenting with acute or subacute nonfamilial ataxia are estimated to have an underlying malignancy [29]. MRI and CT scans are initially normal but often reveal cerebellar atrophy later in the course of the disease. CSF examination shows mild lymphocytic pleocytosis with elevated protein and IgG levels in the first weeks to months. Oligoclonal bands may be present. The diagnosis of PCD is established by demonstration of specific antineuronal antibodies. The type of antibody directs the search for an underlying neoplasm (Table 2).

Antineuronal Antibodies

PCD can be associated with various antineuronal autoantibodies. The clinical and tumor specificities of each of the antibodies are summarized in Table 2.

Anti-Yo (also called PCA-1), anti-Tr (PCA-Tr), and anti-mGluR1 antibodies are associated with relatively “pure” cerebellar syndromes. Anti-Yo antibodies are associated with breast cancer and tumors of the ovaries, endometrium, and fallopian tubes [4, 5, 48]. These antibodies are directed against the cerebellar degeneration–related (CDR) proteins that are expressed by Purkinje cells and the associated tumors [48, 49]. CDR-2–specific cytotoxic T cells have been identified in the serum from patients with PCD, suggesting a pathogenic role for the cellular immune

response in this PNS [14]. Anti-Tr (PCA-Tr) antibodies are directed against an unidentified cytoplasmic Purkinje cell antigen and appear specific for Hodgkin's disease [17]. Anti-mGluR1 antibodies have been found in two patients with PCD and Hodgkin's disease. Passive transfer of patient anti-mGluR1 IgG into CSF of mice induced severe, transient ataxia [25].

Approximately 50% of patients with cerebellar degeneration and underlying SCLC have high titers of anti-Hu antibodies [50]. The remaining patients are likely to have anti-P/Q-type VGCC antibodies. These antibodies were present in all patients who also had LEMS and in some patients with cerebellar degeneration without LEMS. In patients with antiampiphysin or anti-CV2/CRMP5 antibodies, the cerebellar degeneration is often part of the paraneoplastic encephalomyelitis syndrome, and more widespread neurological symptoms and signs are usually found.

The more recently discovered PCA-2 antibody and the ANNA-3 antibody are associated with lung cancer and a variety of neurological syndromes including cerebellar degeneration [36]. Anti-Zic4 antibodies are strongly associated with SCLC, and most patients have paraneoplastic encephalomyelitis, often presenting with cerebellar dysfunction [51]. These patients often have concurrent anti-Hu or anti-CV2/CRMP5 antibodies. Patients with isolated anti-Zic4 antibodies are more likely to develop cerebellar symptoms.

Treatment and Prognosis

The outcome of PCD is generally poor, and the best chance to at least stabilize the syndrome is to treat the underlying tumor [4]. Incidental improvement has been reported either spontaneously or in association with plasma exchange, steroids, i.v. Ig, or rituximab [52]. In patients with anti-Yo–associated cerebellar degeneration, the prognosis is better for patients with breast cancer than for those with gynecologic cancer [5]. The prognosis is better in patients with PCD associated with Hodgkin's disease and anti-Tr (PCA-Tr) or anti-mGluR1 antibodies. With successful treatment of the tumor and/or immunotherapy, symptoms may disappear and the antibodies vanish [17, 25].

Opsoclonus-Myoclonus

Opsoclonus is a disorder of ocular motility that consists of involuntary, arrhythmic, high-amplitude conjugate saccades in all directions. Opsoclonus may occur intermittently or, if more severe, constantly, and it does not remit in the darkness or when the eyes are closed. Opsoclonus is often associated with diffuse or focal myoclonus, the “dancing eyes and dancing feet syndrome,” and other cerebellar and brainstem signs [28, 53, 54]. An excessive startle response reminiscent of hyperekplexia may also occur

in opsoclonus-myoclonus patients [55]. In contrast to most PNS, the course of opsoclonus-myoclonus may be remitting and relapsing [54].

Underlying Tumor

Approximately 20% of adult patients with opsoclonus-myoclonus have a previously undiscovered malignancy [53]. The most commonly associated neoplasms are SCLC and breast and gynecologic cancers [55, 56]. Many other tumors, including thyroid and bladder cancer, have also been reported [57].

Almost 50% of children with opsoclonus-myoclonus have an underlying neuroblastoma. Conversely, approximately 2%–3% of children with neuroblastoma have paraneoplastic opsoclonus-myoclonus [58, 59]. Tumors in children with paraneoplastic opsoclonus-myoclonus apparently have a better prognosis than tumors in patients without this PNS.

Diagnostic Evaluation

MRI scans are usually normal but may show hyperintensities in the brainstem on T2-weighted images [60]. Examination of the CSF may show mild pleocytosis and protein elevation. In some patients, paraneoplastic opsoclonus-myoclonus resembles PCD. The prominent opsoclonus and truncal, rather than appendicular, ataxia distinguish this syndrome from anti-Yo- and anti-Hu-associated PCD [28]. Adult patients with paraneoplastic opsoclonus-myoclonus are older (median age, 66 years) than patients with the idiopathic syndrome (median age, 40 years). In adult patients, the tumor search should be directed at the most common underlying tumors, that is, high-resolution CT of the chest and abdomen, and gynecological examination and mammography (or MRI of the breasts) [56]. When this is negative, FDG-PET should be considered [22, 61].

In children, nonparaneoplastic opsoclonus-myoclonus occurs as a self-limited illness and is probably the result of a viral infection of the brainstem. The search for an occult neuroblastoma should include imaging of the chest and abdomen (CT or MRI scan), urine catecholamine measurements, and metaiodobenzylguanidine scan [62]. When negative, the evaluation should be repeated after several months [63].

Antineuronal Antibodies

Specific antibodies are found in only a minority of patients with paraneoplastic opsoclonus-myoclonus [56]. In women, anti-Ri antibodies (or ANNA-2) are mostly associated with breast and gynecologic tumors. Anti-Ri has occasionally been found in bladder cancer and SCLC and may then occur in male patients [28, 57]. Anti-Ri anti-

bodies are directed against the Nova proteins [64, 65]. Paraneoplastic opsoclonus-myoclonus can also be associated with anti-Hu antibodies, usually as part of a more widespread paraneoplastic encephalomyelitis. Bataller et al. [66] screened a brainstem cDNA library with sera from 21 patients with (paraneoplastic) opsoclonus-myoclonus. Twenty-five proteins were identified, recognized by one or two sera each, demonstrating that immunity to neuronal autoantigens in opsoclonus-myoclonus is both frequent and heterogeneous.

In children presenting with opsoclonus-myoclonus, the detection of anti-Hu antibodies is diagnostic of an underlying neuroblastoma [67]. The frequency of anti-Hu antibodies in neuroblastoma with paraneoplastic opsoclonus-myoclonus is approximately 10% [67–69]. This finding differs little from the 4%–15% of anti-Hu positive sera in children with neuroblastoma who do not have opsoclonus-myoclonus [67, 68].

Treatment and Prognosis

In contrast to most of the other PNS, paraneoplastic opsoclonus-myoclonus may remit either spontaneously, following treatment of the tumor, or in association with clonazepam or thiamine treatment. Most patients with idiopathic opsoclonus-myoclonus make a good recovery that seems to be accelerated by steroids or i.v. Ig. Paraneoplastic opsoclonus-myoclonus usually has a more severe clinical course, and treatment with steroids or i.v. Ig appears ineffective. In a series of 14 patients with paraneoplastic opsoclonus-myoclonus, eight patients whose tumors were treated showed complete or partial neurological recovery. In contrast, five of the six patients whose tumors were not treated died of the neurological syndrome despite steroids, i.v. Ig, or plasma exchange [56]. However, improvement following the administration of steroids, cyclophosphamide, azathioprine, i.v. Ig, plasma exchange, or plasma filtration with a protein A column has been described in single cases [55, 70–72].

In children, paraneoplastic opsoclonus-myoclonus may improve following treatment with adrenocorticotrophic hormone, prednisone, azathioprine, or i.v. Ig, but residual central nervous system signs are frequent [59, 63, 73]. Treatment of the tumor with chemotherapy is the most important predictor of good neurological recovery [74].

Subacute Sensory Neuronopathy

Subacute sensory neuronopathy is an uncommon disorder that is probably paraneoplastic in about 20% of patients [75, 76]. The symptoms begin with pain and paraesthesia. Clumsiness and unsteady gait then develop and usually become predominant. The distribution of symptoms is often asymmetrical or multifocal. The upper limbs are often

affected first and are almost invariably involved with evolution. Sensory loss may also affect the face, chest, or abdomen. On examination, all sensory modalities are affected, but the most striking abnormality is loss of deep sensation causing sensory ataxia with pseudoathetosis of the hands. Tendon reflexes are depressed or absent. In most patients, the disease progresses rapidly over weeks to months, leaving the patient severely disabled. In a few patients, the neuropathy remains stable for months with mild neurological deficits [77]. Subacute sensory neuropathy occurs in approximately 75% of patients with paraneoplastic encephalomyelitis, is predominant in 50%, and is clinically pure in 25% [2, 3]. Autonomic neuropathy, including gastrointestinal pseudo-obstruction, is common.

Underlying Tumor

Subacute sensory neuropathy is associated with lung cancer, usually SCLC, in 70%–80% of patients [2, 3, 31]. Other associated tumors include breast cancer, ovarian cancer, sarcoma, and Hodgkin's lymphoma [75, 76]. Subacute sensory neuropathy usually predates the diagnosis of cancer, with a median delay of 3.5–4.5 months [2, 3].

Diagnostic Evaluation

Electrophysiologically, the hallmark of subacute sensory neuropathy is the absence of, or marked reduction in, sensory nerve action potentials. Motor conduction velocities may be mildly reduced. Early in the course of the disease, CSF examination shows mild pleocytosis, with an elevated IgG level and oligoclonal bands [3, 75, 76]. Sural nerve biopsy is rarely required for the diagnosis but may differentiate this disorder from vasculitic neuropathy.

Antineuronal Antibodies

Anti-Hu is the most frequent paraneoplastic antibody in subacute sensory neuropathy [2, 3, 30, 31]. In this setting, anti-Hu antibody detection has a specificity of 99% and sensitivity of 82% [78]. The absence of anti-Hu antibodies does not rule out an underlying cancer. Anti-CRMP5/CV2 antibodies also occur with paraneoplastic peripheral neuropathies [79]. These patients usually have a sensory or sensorimotor neuropathy, with less frequent involvement of the arms but often associated with cerebellar ataxia [16, 79, 80]. Anti-CRMP5/CV2 antibodies are usually associated with SCLC, neuroendocrine tumors, and thymoma. Anti-amphiphysin antibodies are associated with multifocal paraneoplastic encephalomyelitis, and symptoms often include sensory or sensorimotor neuropathy [34, 81, 82]. Associated tumors (mostly limited) are mainly SCLC, breast cancer, and melanoma.

Treatment and Prognosis

Immunotherapy consisting of plasma exchange, steroids, and i.v. Ig is ineffective in most cases [27, 83]. There may be some exceptions to this rule [23, 84]. In one study, 2 of 10 patients stabilized in relatively good clinical condition following intensive treatment with a combination of steroids, cyclophosphamide, and i.v. Ig [23]. Early detection and treatment of the underlying neoplasm, usually SCLC, appears to offer the best chance of stabilizing the neurological symptoms [3, 27]. In patients with an identifiable tumor, antitumor treatment is recommended. In the absence of a tumor, antitumor treatment may be considered in patients with anti-Hu antibodies, age >50 years, and with a history of smoking. In patients not receiving antitumor therapy, a short course of immunotherapy can be considered.

Symptomatic treatment is directed at neuropathic pain and dysautonomic symptoms such as orthostatic hypotension.

LEMS

Patients with LEMS present with proximal weakness of the lower extremities and fatigability. Bulbar symptoms may occur more frequently than previously reported [85] but are generally milder than with myasthenia gravis. Respiratory weakness can occur. Deep tendon reflexes, especially those in the legs, are diminished or absent but may reappear after exercise. Autonomic features, especially dryness of the mouth, impotence, and mild/moderate ptosis, ultimately develop in 95% of patients [85–87]. In some patients, LEMS may develop in association with other PNS, including PCD and encephalomyelitis [50].

Underlying Tumor

Approximately 70% of patients have cancer, almost always SCLC [86, 88]. Other tumors include small cell carcinomas of the prostate and cervix, lymphomas, and adenocarcinomas. The prevalence of LEMS in patients with SCLC is estimated to be around 3% [87, 89]. Clinically and serologically, the 30% without identifiable tumors are indistinguishable from the paraneoplastic LEMS patients, although LEMS may have a more progressive course in patients with SCLC [85]. In patients presenting with LEMS, a smoking history and absence of the HLA-B8 genotype strongly predict underlying SCLC [90]. Patients with SCLC and LEMS survive significantly longer than SCLC patients who do not have this PNS [91].

Diagnostic Evaluation

The typical pattern of electromyographic abnormalities is the hallmark of LEMS. This includes a low compound muscle action potential at rest with a decreased response at

low rates of repetitive stimulation (3 Hz) and an incremental response at high rates of repetitive stimulation (50 Hz) or 15–30 seconds of maximal voluntary contraction [92].

Antineuronal Antibodies

Most patients with LEMS have antibodies against P/Q-type calcium channels that are located presynaptically in the neuromuscular junction [92]. About 20% have anti-MysB antibodies reactive with the β subunit of neuronal calcium channels [93].

Treatment and Prognosis

Treatment of LEMS must be tailored to the individual based on severity of the symptoms, underlying disease, life expectancy, and previous response to treatment. In patients with paraneoplastic LEMS, treatment of the tumor frequently leads to neurological improvement [94]. Symptomatic treatment is with drugs that facilitate the release of acetylcholine from motor nerve terminals, such as 3,4-diaminopyridine (DAP) [95]. In a placebo-controlled randomized trial, DAP (5–20 mg three to four times daily) was effective for long-term treatment, alone or in combination with other treatments [96]. The maximum recommended daily dose of DAP is 80 mg; at higher doses, seizures occur [96]. Cholinesterase inhibitors (pyridostigmine, 30–60 mg, every 6 hours) may improve dryness of the mouth but rarely relieve weakness. If these treatments are not effective enough, it must be decided if immunosuppressive therapy with steroids, azathioprine, or cyclosporine is appropriate. Removal of the pathogenic anti-P/Q-type calcium channel antibodies by plasma exchange [97] and i.v. Ig can give quick but transient relief [86, 98]. LEMS responds less favorably to immunotherapy than myasthenia gravis.

Dermatomyositis

In dermatomyositis, the characteristic heliotrope rash (purplish discoloration of the eyelids) often precedes the

appearance of proximal muscle weakness. Other manifestations include arthralgia, myocarditis and congestive heart failure, and interstitial lung disease. Clinical, electromyographical, and pathological findings of dermatomyositis are similar in patients with and without cancer.

Underlying Tumor

The standardized incidence ratio for a malignant disease in dermatomyositis is 6.2 (95% confidence interval, 3.9–10.0) [99]. Dermatomyositis is associated with cancer of the ovary, lung, pancreas, stomach, colorectum, and breast, and with non-Hodgkin's lymphoma [100].

Diagnostic Evaluation

Most patients have elevated serum creatine kinase levels and electromyographic evidence of myopathy. Muscle imaging (CT or MRI) may help in confirming the diagnosis and determining the type of inflammatory myopathy and in selecting an appropriate biopsy site. Muscle or skin biopsy is the definitive diagnostic procedure and shows inflammatory infiltrates [101].

Antineuronal Antibodies

Antibodies to the Mi-2 protein complex are specific for dermatomyositis and are present in high titers in about 35% of cases [102].

Treatment and Prognosis

Treatment of paraneoplastic dermatomyositis is generally the same as for patients without a tumor. Nearly all patients respond to corticosteroids [103]. Refractory patients and patients requiring a lower dose of steroids can be treated with azathioprine. Methotrexate and cyclophosphamide may also be considered [103].

DISCLOSURE OF POTENTIAL CONFLICTS OF INTEREST

The authors indicate no potential conflicts of interest.

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Janet W. de Beukelaar and Peter A. Sillevs Smitt

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