

EFNS TASK FORCE ARTICLE

Management of paraneoplastic neurological syndromes: report of an EFNS Task Force

C. A. Vedeler^{a,b}, J. C. Antoine^c, B. Giometto^d, F. Graus^e, W. Grisold^f, I. K. Hart^g, J. Honnorat^h, P. A. E. Sillevs Smittⁱ, J. J. G. M. Verschuuren^j and R. Voltz^k for the Paraneoplastic Neurological Syndrome Euronetwork

^aDepartment of Neurology, Haukeland University Hospital, Bergen, Norway; ^bDepartment of Clinical Medicine, University of Bergen, Bergen, Norway; ^cDepartment of Neurology, Hopital Bellevue, Saint Etienne, France; ^dDepartment of Neurology and Psychiatry (2Neurologic Clinic) University of Padua, Padua, Italy; ^eService of Neurology, Institut d'Investigacio Biomedica August Pi i Sunyer (IDIBAPS), Hospital Clinic, University of Barcelona, Barcelona, Spain; ^fLudwig Boltzmann Institut fur Neuroonkologie, Vienna, Linz, Austria; ^gNeuroimmunology Group, Department of Neurological Science, Liverpool, UK; ^hAtaxia Research Center, Neurology B, Hospital Neurologique, Lyon, France; ⁱDepartment of Neurology, Erasmus University Medical Center, Rotterdam, The Netherlands; ^jDepartment of Neurology, Leiden University Medical Center, Leiden, The Netherlands; and ^kDepartment of Palliative Medicine, University of Cologne, Cologne, Germany

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Paraneoplastic neurological syndromes (PNS) are remote effects of cancer on the nervous system. An overview of the management of classical PNS, i.e. paraneoplastic limbic encephalitis, subacute sensory neuronopathy, paraneoplastic cerebellar degeneration, paraneoplastic opsoclonus-myoclonus, Lambert–Eaton myasthenic syndrome and paraneoplastic peripheral nerve hyperexcitability is given. Myasthenia gravis and paraproteinemic neuropathies are not included in this report. No evidence-based recommendations were possible, but good practice points were agreed by consensus. Urgent investigation is indicated, especially in central nervous system (CNS) syndromes, to allow tumour therapy to be started early and prevent progressive neuronal death and irreversible disability. Onconeural antibodies are of great importance in the investigation of PNS and can be used to focus tumour search. PDG-PET is useful if the initial radiological tumour screen is negative. Early detection and treatment of the tumour is the approach that seems to offer the greatest chance for PNS stabilization. Immune therapy usually has no or modest effect on the CNS syndromes, whereas such therapy is beneficial for PNS affecting the neuromuscular junction. Symptomatic therapy should be offered to all patients with PNS.

Background

Paraneoplastic neurological syndromes (PNS) were initially defined as neurological syndromes of unknown cause that often antedate the diagnosis of an underlying, usually not clinically evident, cancer. In the last two decades, the discovery that many PNS are associated with antibodies against neural antigens expressed by the tumour (onconeural antibodies), has suggested that some PNS are immune mediated. PNS are rare and occur in < 1% of patients with cancer. However, the diagnosis and treatment is important because the disability caused by PNS is often severe and the correct diagnosis usually leads to the discovery of a small tumour with a chance of being cured. Recently, recommended diagnostic criteria for PNS have been published by the PNS Euronetwork

[1]. In this paper the EFNS Task force, as part of the PNS Euronetwork, has outlined guidelines for the management of classical PNS.

Methods

The Task Force considered the different syndromes known as paraneoplastic and chose to focus on classical PNS [1]: paraneoplastic limbic encephalitis (PLE), subacute sensory neuronopathy (SSN), paraneoplastic cerebellar degeneration (PCD) and paraneoplastic opsoclonus-myoclonus (POM), as well as Lambert–Eaton myasthenic syndrome (LEMS) and paraneoplastic peripheral nerve hyperexcitability (PPNH) (Table 1). Myasthenia gravis has not been included and will be reported together with a broader overview of LEMS and PNH in a separate Task Force report on treatment of neuromuscular disorders. Paraproteinemic neuropathies have previously been evaluated by an EFNS Task force [2]. Paraneoplastic retinopathy and dermatomyositis

Correspondence: Christian A. Vedeler, Department of Neurology, Haukeland University Hospital, Bergen, Norway (tel.: 47 55 97 5044; fax: 47 55 97 5164; e-mail: christian.vedeler@helse-bergen.no).

Table 1 Paraneoplastic neurological syndromes and their therapy

Paraneoplastic syndrome	Common associated tumours	Onconeural antibodies	Response to symptomatic therapy	Response to immunotherapy	Response to tumour therapy
Limbic encephalitis	SCLC Testicular Breast Hodgkin's Thymoma	Hu Ma2 CV2/CRMP5 Amphiphysin VGKC, but not specific for paraneoplasia	Yes	Variable. Ma2 and onconeural antibody negative patients seem to respond best	Yes, patients often stabilize if treated early
Subacute sensory neuronopathy	SCLC Breast Ovarian Sarcoma Hodgkin's	Hu CV2/CRMP5	Yes	Rare	Yes, especially when treated early
Cerebellar degeneration	Ovary Breast SCLC Hodgkin's	Yo Hu Tr CV2/CRMP5 VGCC, but not specific for paraneoplasia	Yes	Rare	Yes, especially in Hodgkin's
Opsoclonus-myoclonus	Lung Breast Gynaecological Melanoma Histiocytoma Neuroblastoma in children	Ri Hu Ma2 Amphiphysin Often none, especially in children	Yes	Occasionally in adults. Often in children	Yes
Lambert–Eaton myasthenic syndrome	SCLC	VGCC, but not specific for paraneoplasia	Yes	Yes	Yes
Peripheral nerve hyperexcitability	Thymoma SCLC Non-SCLC Hodgkin's Plasmacytoma	VGKC, but not specific for paraneoplasia	Yes	Yes	Yes

SCLC, small cell lung cancer.

have not been included in this report. Search strategies have included English literature from the following databases: Cochrane Library, MedLine, PubMed (last search 15 December 2004). The key words used for the search included 'limbic encephalitis', 'sensory neuronopathy', 'cerebellar ataxia', 'opsoclonus-myoclonus', 'Lambert–Eaton myasthenic syndrome', 'neuromyotonia' in combination with 'investigation' and 'therapy'. All evidence available was evaluated as class IV – case reports, case series and expert opinion [3]. Thus, no recommendations reach level A, B or C [3]. However, good practice points were agreed by consensus.

Paraneoplastic limbic encephalitis

Clinical features

Paraneoplastic limbic encephalitis is characterized by the acute, or subacute, onset of symptoms that suggest

involvement of the limbic system. Patients may develop short-term memory loss or amnesia, become disoriented, or may show psychosis including visual or auditory hallucinations, or paranoid obsession. Confusion, depression and anxiety are also common. Generalized or partial complex seizures are seen in about 50% of patients. In the majority of patients, the symptoms antedate the diagnosis of a tumour by a mean of 3–5 months. PLE is preferentially associated with small cell lung cancer (SCLC) (40%), germ cell tumours of the testis (20%), breast cancer (8%), Hodgkin's lymphoma, thymoma and immature teratoma [4].

Investigation

Magnetic resonance imaging (MRI) alterations in PLE are seen in about 60% of patients, but the figure is probably much higher if FLAIR sequences are included in the study. The MRI features are most evident on

coronal sections and typically consist of abnormal high-signal intensity on T2 sequences in one or both medial temporal lobe(s). On T1 sequences the temporal-limbic area may be hypointense and atrophic and rarely enhance with contrast injection [5]. In the absence of MRI abnormalities, FDG-PET studies should show an increased tracer activity in the medial temporal lobe, which may reflect an acute stage of the inflammatory process [6]. In 45% of patients, EEG reveals epileptic abnormalities from the temporal lobe, but in the majority of patients it shows unilateral or bilateral temporal slow waves. Cerebrospinal fluid (CSF) examinations show inflammatory signs (e.g. pleocytosis and oligoclonal bands) in about 60% of patients.

Onconeural antibodies may be found in the serum and CSF of about 60% of patients with PLE. The most frequent onconeural antibodies are anti-Hu, anti-Ma2 (with or without anti-Ma1), anti-CV2/CRMP5 and anti-amphiphysin. Seventy-eight per cent of patients with PLE and anti-Hu have symptoms that suggest a dysfunction in areas of the nervous system other than the limbic system. In fact, PLE may be the presenting or the predominant disorder of patients with paraneoplastic encephalomyelitis (PEM) or the 'anti-Hu syndrome'. These patients usually are older than 40 years, and the related tumour is SCLC.

Patients with only Ma2 antibodies are usually male, younger than 40 years and clinically present with symptoms of diencephalic and upper brainstem dysfunction. The MRI evaluation is more likely to present abnormalities in medial temporal lobes, hypothalamus, basal ganglia, thalamus or upper brainstem collicular region [7]. CV2/CRMP5 antibodies are instead detected in patients with thymoma or SCLC [8]. VGKC antibodies can be associated with PLE and thymoma or with non-paraneoplastic LE [9–11].

Patients older than 40 years, smokers and with Hu antibody have to be investigated for the presence of SCLC. Anti-Hu-positive patients could also have extrathoracic tumours, but these can only be considered responsible for PLE when they express Hu antigens [12]. The absence of Hu antibody does not rule out the presence of SCLC. However, in patients older than 40 years, and without onconeural antibodies, the more frequently associated tumours are breast cancer, non-SCLC tumours and thymoma. Imaging studies to detect SCLC include high resolution computed tomography (CT) of the chest and PDG-PET if the CT scan is negative [13,14]. Special attention must be paid to abnormal lymph nodes in the mediastinum. Bronchoscopy is usually negative. In male patients younger than 40 years, the detection of Ma2 antibodies suggests the presence of testicular cancer which should be evaluated with ultrasound.

Therapy

Early detection and treatment of the underlying tumour is the approach that offers the greatest chance for neurological improvement or symptom stabilization. In men with only Ma2 antibodies elective orchidectomy and serial examination of the testicle to rule out *in situ* carcinomas is indicated in patients at high risk of testicular cancer such as the presence of calcifications or undescended testicle. The increasing evidence that PLE is immune mediated has prompted the use of immune therapies. There are no reports that indicate which kind of immune therapy should be used. Patients are usually treated with one or more of the following: intravenous immunoglobulin, plasma exchange or steroids [4]. PLE without onconeural antibodies and those with Ma2 antibodies (with or without anti-Ma1) seem to respond better to immune therapy [4]. Symptomatic therapy of PLE is directed against epilepsy and psychiatric symptoms.

Subacute sensory neuronopathy

Clinical features

Several neuropathies have been reported as paraneoplastic, but only SSN is regarded as a classical PNS [1]. SSN is associated with SCLC in 70–80% of cases, but may also occur with breast cancer, ovarian cancer, sarcoma or Hodgkin's disease [15]. SSN precedes the overt clinical manifestations of the cancer with a median delay of 4.5 months [12]. The onset of SSN is usually subacute and rapidly progressive over weeks before a plateau phase is reached. The distribution is frequently multifocal or asymmetrical. Symptoms consist of pain and paraesthesiae [12]. Upper limbs are usually affected first or almost invariably involved with the evolution. Sensory loss, especially affecting deep sensation, often leads to severe sensory ataxia and tendon reflexes are absent. Sensory loss may also affect the face, chest or abdomen. Many patients become bedridden, but an indolent course has been reported [16]. SSN occurs in 74% of patient with PEM and is predominant in 50–60% and clinically pure in 24% [12]. Autonomic neuropathy including digestive pseudo-obstruction is frequent.

Investigation

Cerebrospinal fluid analysis may show elevated protein concentration, pleocytosis and sometimes oligoclonal bands. Electrophysiologically, the hallmark is a severe and diffuse alteration of sensory nerve action potentials that are either absent or markedly reduced [17]. Motor

conduction velocities can be mildly altered. Nerve biopsy is usually not necessary, but may sometimes be helpful in distinguishing SSN from multiple mono-neuropathy because of vasculitis [18].

Hu antibodies are most often associated with SSN. Their estimated specificity in the diagnosis of cancer in patients suspected to have SSN is 99%, but the sensitivity is 82% [19]. The absence of Hu antibodies does not exclude the presence of an underlying cancer. CV2/CRMP5 antibodies also occur with peripheral neuropathies [20]. In this setting, the neuropathy is usually sensory or sensori-motor in which upper limbs are less frequently involved, but often associated with cerebellar ataxia [8,21]. The electrophysiological pattern is axonal or mixed axonal and demyelinating. SCLC, neuroendocrine tumours and thymoma are usually associated with CV2/CRMP5 antibodies. When high resolution CT of the chest is negative, FDG-PET is recommended [13,14].

Therapy

In a retrospective study of 200 patients with PEM/SSN, treatment of the tumour was an independent predictor of improvement and stabilization of the neurological disorder [12] suggesting that an early diagnosis of the cancer may give the patients the best chance of stabilizing the neurological disorder. Although occasional reports indicate that immunosuppressive treatment might benefit patients with SSN and Hu antibodies, a larger series failed to demonstrate a clear benefit of intravenous immunoglobulin, steroids, plasma exchange or cyclophosphamide, alone or in combination [22]. Symptomatic treatment is directed against neuropathic pain, sensory ataxia and dysautonomic manifestation such as orthostatic hypotension.

Paraneoplastic cerebellar degeneration

Clinical features

Paraneoplastic cerebellar degeneration is characterized by subacute development of a severe pancerebellar dysfunction. Cerebellar signs usually begin with gait ataxia and, over a few weeks or months, progress to severe, usually symmetrical truncal and limb ataxia, with dysarthria and often nystagmus [23]. Occasionally the onset is rapid, within a few hours or days. Vertigo is common, and many patients complain of diplopia. The cerebellar deficit usually stabilizes, but, the patient is then often severely incapacitated and most become bedridden in the first 3 months after diagnosis. PCD is preferentially associated with ovarian cancer, breast cancer, SCLC or Hodgkin's disease.

Investigation

Brain MRI studies are initially normal, but can demonstrate cerebellar atrophy in the latter stages of the disease. CSF examination shows inflammatory signs without cancer cells (e.g. pleocytosis and oligoclonal bands) in about 60% of PCD patients.

Yo antibodies are most frequently associated with PCD. These patients are mainly female with an average age of 61 years. The associated cancer is ovary, breast or other gynaecological malignancies. Patients with Hu antibodies differ from those with anti-Yo in terms of a frequent association with SCLC, the same frequency in male and female, and often other neurological manifestations as part of PEM [12]. Between 13 and 20% of patients with Hu antibodies present with a subacute cerebellar syndrome that, in the initial stage, cannot be differentiated from PCD [12]. Neuropathy is observed in 60% of patients with PCD and CV2/CRMP5 antibodies [8,21] and such antibodies are observed in about 7% of patients with PCD [24]. Patients with CV2/CRMP5 antibodies are mainly male (70%) with an average age of 62 years. The most frequently associated tumour is SCLC (60%). Tr antibodies are markers of patients with PCD and Hodgkin's disease, which is the third most common associated cancer with PCD, after SCLC and ovarian cancer. Unlike other antibodies, anti-Tr usually disappears after treatment of the tumour or, in a few patients, are only found in the CSF [25]. Ri antibodies are mainly observed in patients with cerebellar ataxia and POM. The associated cancers are breast or lung cancer. Some cases of PCD have been reported in association with antibodies against amphiphysin, Ma2, Zic4, mGluR1 or VGCC [1,26,27]. When VGCC antibodies are present, LEMS can be associated with PCD [24,28]. The absence of onconeural antibodies cannot rule out the diagnosis of PCD, as only 50% of patients with PCD harbour such antibodies [24].

If SCLC is suspected, the tumour is generally demonstrated by high resolution CT of the chest. Special attention must be paid to abnormal lymph nodes in the mediastinum. Bronchoscopy is usually negative. The use of FDG-PET should be reserved to patients with onconeural antibodies when conventional imaging fails to identify a tumour [13,14]. In patients without onconeural antibodies the sensitivity and specificity of FDG-PET is poorer. If a gynaecological tumour is suspected careful breast and pelvic examination, mammography and pelvic CT are recommended. If no malignancy is revealed with this initial work-up, surgical exploration and removal of ovaries may be warranted, particularly in postmenopausal women with Yo antibodies [23].

Therapy

The best chance to at least stabilize the syndrome is to treat the underlying tumour [27]. Immune therapy is rarely effective, but there have been reports of an improvement in few patients after the administration of intravenous immunoglobulin, steroids or plasmapheresis [22,29,30]. Patients with anti-Tr and Hodgkin's disease are more likely to improve than those with other antibodies [25]. In patients with Yo antibodies, the prognosis is worse in patients with ovarian cancer and better in patients with breast cancer [31]. The prognosis is also better in PCD patients without onconeural antibodies than in patients with Hu antibodies [24]. Symptomatic treatment of cerebellar ataxia includes neurorehabilitation with speech and swallowing therapy, and modest additional gains can be seen with propranolol or antiepileptic drugs.

Paraneoplastic opsoclonus-myoclonus

Clinical features

Opsoclonus means involuntary eye movements in any direction. It does not remit in darkness and with eyes closed and may occur intermittently or, if more severe, constantly. In POM, opsoclonus is often accompanied by cerebellar signs such as gait ataxia and limb myoclonus, the so-called 'dancing eyes, dancing feet syndrome' and encephalopathy [32–34]. In contrast to most paraneoplastic syndromes, the course of POM may be remitting and relapsing [32,35].

In infants, the most common associated tumour is neuroblastoma [36,37]. In adults it is either lung cancer, breast cancer or a gynecological cancer such as ovary or uterus [38–40]. The association with other tumours on single case basis has been reported, such as melanoma [41] or malignant fibrous histiocytoma [42].

Investigation

Brain MRI studies are normal whilst examination of the CSF may show mild pleocytosis and protein elevation. Most infant [43,44] and adult patients do not harbour a clearly defined onconeural antibody [38,45]. In those who do, anti-Hu, anti-amphiphysin, anti-Ri or anti-Ma2 may be found [38,46–48].

In children, the search for an occult neuroblastoma should include imaging of chest and abdomen (CT scan or MRI), urine catecholamine measurements (VMA and HVA) and metaiodobenzylguanidine scan [49]. When negative, the evaluation should be repeated after several months [50].

Initial investigation in adult patients suspected of POM should be directed at tumours associated with this condition, i.e. high resolution CT of the chest and abdomen and gynaecological examination and mammography in women [38]. When this evaluation is negative, FDG-PET should be considered [13,14].

Therapy

Tumour therapy is the mainstay of management [38]. In the paediatric population, POM may improve following treatment with adrenocorticotrophic hormone, steroids, or intravenous immunoglobulin, but residual CNS signs are frequent [36,50,51]. In contrast to idiopathic OM, no clear advantage of immune therapy has been demonstrated in adult POM [38]. Improvement following the administration of steroids, cyclophosphamide, azathioprine, intravenous immunoglobulin, plasma exchange or plasma filtration with a protein A column has been described in single cases [35,52–54]. Symptomatic therapy of nystagmus and oscillopsia includes the use of various anti-epileptic drugs, baclofen or propranolol [34]. Myoclonus can be treated with anti-epileptic drugs.

Lambert–Eaton myasthenic syndrome

Clinical features

In more than 90% of the patients, muscle weakness starts proximal in the legs. Weakness can spread to other skeletal muscles in a caudo-cranial order, but only rarely leads to the need for artificial respiration. Ptosis and ophthalmoplegia tend to be milder than in myasthenia gravis [54]. Autonomic dysfunction is characterized by the presence of a dry mouth, dryness of the eyes, blurred vision, impotence, constipation, impaired sweating or orthostatic hypotension [55]. Autonomic dysfunction is mostly mild to moderate, in contrast to the severe disabling autonomic dysfunction sometimes found in SSN/PEM. In rare cases, patients with LEMS and SCLC develop PCD [24–28].

Investigation

Electrophysiological studies show a reduced amplitude of the compound muscle action potential after nerve stimulation with decrement at low frequency stimulation (3 Hz) of more than 10%, and an increment of more than 100% after maximum voluntary contraction of the muscle for 15 s. High frequency stimulation at > 20 Hz also produces an increased increment, but is painful and not usually necessary. Anti-P/Q-type VGCC antibodies are present in the serum of at least

85% of the patients [56]. These antibodies are found in both forms of LEMS, with or without SCLC. Antibodies to N-type VGCC have also been found in the serum, but their contribution to the muscle weakness or autonomic dysfunction is probably small. They are not used for diagnostic purposes.

In half of the LEMS patients, SCLC will be found, mostly within 2 years. A retrospective study of 77 patients with LEMS, showed that patients who had been smoking and were HLA-B8-negative had a 69% chance of developing SCLC. By contrast, none of the 24 patients who never smoked and were HLA-B8-positive developed SCLC [57]. However, it is recommended that all patients are examined by high resolution chest CT, and possibly also by bronchoscopy and PDG-PET if the CT scan is negative. This is especially important for patients with a high risk of SCLC (smoking and HLA-B8 negative). Follow-up should be continued with CT scans every 6 months for at least 4 years.

Therapy

For patients with SCLC it is important to treat the tumour. Specific tumour therapy in a small retrospective series resulted in recovery from the neurological syndrome within 6–12 months [58]. One patient remained tumour free after radiotherapy and local resection at 12 years. Chemotherapy which is the first choice of tumour treatment, will also have an immunosuppressive effect on LEMS. It has been shown that the presence of LEMS in patients with SCLC improves survival [59]. Symptomatic treatment consists of 3,4-diaminopyridine [60] and additional therapeutic effect may be obtained if combined with pyridostigmin. If this treatment is not sufficient, steroids, azathioprine, plasma exchange and intravenous immunoglobulin should be considered.

Paraneoplastic peripheral nerve hyperexcitability

Clinical features

The commonest form of PNH (neuromyotonia; Isaacs' syndrome) is autoimmune and often caused by antibodies to VGKC [61]. PPNH is present in up to 25% of the patients and can predate the detection of a tumour by up to 4 years [62]. In a study of 60 patients, seven (12%) had a thymoma with myasthenia gravis (MG), two (3%) had a thymoma without clinical MG, four (7%) had an SCLC and one (2%) had a lung adenocarcinoma [62]. PPNH can also occur with Hodgkin's disease [63,64] and plasmacytoma [65].

The clinical hallmark of PNH is spontaneous and continuous skeletal muscle overactivity usually presenting as twitching and painful cramps and often accompanied by various combinations of stiffness, pseudomyotonia, pseudotetany and weakness [66]. About 33% of patients also have sensory features and up to 50% have hyperhidrosis suggesting autonomic involvement. CNS features can occur, ranging from personality change and insomnia to a psychosis with delusions, hallucinations and autonomic disturbance (Morvan's syndrome).

Investigation

EMG helps to confirm PNH and excludes other causes of continuous muscle overactivity such as the stiff limb syndromes [66]. Nerve conduction studies may characterize an underlying peripheral neuropathy [62,66].

There is no antibody that indicates whether PNH is paraneoplastic. VGKC antibodies are found in about 35% of all acquired PNH patients, although this rises to 80% in those with thymoma [61]. VGKC antibodies can also be associated with PLE and thymoma without PNH, or with non-paraneoplastic LE [9–11]. Hu antibodies can be helpful as one PPNH patient had SCLC [67]. Serum and urine screening for a paraprotein can help identify a plasmacytoma [65].

Most adults warrant a post-contrast CT mediastinum scan as up to 15% of patients have a thymoma, sometimes in the absence of MG or AChR antibodies [62]. This is combined with a high resolution CT of the chest as about 10% of PNH patients will have SCLC or adenocarcinoma [62]. Chest CT may also help detect Hodgkin's disease [63,64]. When the initial tumour screen is negative and malignancy is still suspected, PDG-PET is the investigation of choice. Monitoring for up to 4 years is indicated in those at risk of lung cancer [62].

Treatment

Paraneoplastic peripheral nerve hyperexcitability often improves and can remit after treatment of cancer [63, 65–67]. The demonstration that most cases of PNH are autoimmune has led to trials of immunomodulatory therapies in patients, including a few with thymoma [66,68] whose symptoms are debilitating or refractory to symptomatic therapy. Plasma exchange often produces useful clinical improvement lasting about 6 weeks accompanied by a reduction in EMG activity [66] and a fall in VGKC antibody titres [69]. Experience suggests that intravenous immunoglobulin can also help [70] despite reports that it worsened PNH in one patient [71] and was less effective than plasma exchange in another

[72]. By analogy with LEMS, selected patients with severe PPNS refractory to other treatments may benefit from serial immunomodulatory therapy every 6–8 weeks.

Prednisolone, with or without azathioprine or methotrexate, has been useful in selected autoimmune PNH patients [66,73] including a few patients with thymoma-associated PPNH who did not improve after thymectomy [66]. All forms of PNH, including paraneoplastic, usually improve with symptomatic treatment using various anti-epileptic drugs [66].

Recommendations as good practice points

- Patients with PNS most often present with neurological symptoms before an underlying tumour is detected. Onconeural antibodies should be sought in sera from patients with suspected PNS. The antibodies are important for diagnosis and tumour search.
- Radiological investigations for tumours, such as high resolution CT for the detection of SCLC, are important, but should be followed by PDG-PET if no tumour is found.
- Patients should also be followed at regular intervals, for example every 6 months for up to 4 years, to search for tumour in cases where the initial tumour screen was negative.
- Early detection and treatment of the tumour is the approach that seems to offer the greatest chance for PNS stabilization. This is carried out in cooperation with the oncologist, pulmonologist, gynaecologist or paediatrician depending on the associated tumour.
- Immune therapy (steroids, plasma exchange or intravenous immunoglobulin) usually has no or modest effect on PLE, SSN or PCD.
- Children with POM may respond to immune therapy, whereas no clear evidence of such therapy has been shown in adults with POM.
- Patients with LEMS or PPNH usually improve with immune therapy.
- Symptomatic therapy should be offered to all patients with PNS.

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References

1. Graus F, Delattre JY, Antoine JC, *et al.* Recommended diagnostic criteria for paraneoplastic neurological syndromes. *Journal of Neurology, Neurosurgery and Psychiatry* 2004; **75**: 1135–1140.
2. Willison HJ, Ang W, Gilhus NE, *et al.* EFNS Task force report: a questionnaire-based survey on the service provision and quality assurance for determination of diagnostic autoantibody tests in European neuroimmunology centres. *European Federation of Neurological Societies. European Journal of Neurology* 2000; **7**: 625–628.
3. Brainin M, Barnes M, Baron J-C, *et al.* Guidance for the preparation of neurological management guidelines by EFNS scientific task forces – revised recommendations 2004. *European Journal of Neurology* 2004; **11**: 577–581.
4. Gultekin SH, Rosenfeld MR, Voltz R, *et al.* Paraneoplastic limbic encephalitis: neurological symptoms, immunological findings and tumor association in 50 patients. *Brain* 2000; **123**: 1481–1494.
5. Dirr LY, Elster AD, Donofrio PD, Smith M. Evolution of brain abnormalities in limbic encephalitis. *Neurology* 1990; **40**: 1304–1306.
6. Provenzale JM, Barboriak DP, Coleman RE. Limbic encephalitis: comparison of FDG PET and MRI findings. *American Journal of Roentgenology* 1998; **18**: 1659–1660.
7. Dalmau J, Graus F, Villarejo A, *et al.* Clinical analysis of anti-Ma2-associated encephalitis. *Brain* 2004; **127**: 1831–1844.
8. Yu Z, Kryzer TJ, Grisemann GE, *et al.* CRMP-5 neuronal autoantibody: marker of lung cancer and thymoma-related autoimmunity. *Annals of Neurology* 2001; **49**: 146–154.
9. Buckley C, Oger J, Clover L, *et al.* Potassium channel antibodies in two patients with reversible limbic encephalitis. *Annals of Neurology* 2001; **50**: 74–79.
10. Pozo-Rosich P, Clover L, Saiz A, *et al.* Voltage-gated potassium channel antibodies in limbic encephalitis. *Annals of Neurology* 2003; **54**: 530–533.
11. Vincent A, Buckley C, Schott JM, *et al.* Potassium channel antibody-associated encephalopathy: a potentially immunotherapy-responsive form of encephalitis. *Brain* 2004; **127**: 701–712.
12. Graus F, Keime-Guibert F, Reñe R, *et al.* Anti-Hu-associated paraneoplastic encephalomyelitis: analysis of 200 patients. *Brain* 2001; **124**: 1138–1148.
13. Linke R, Schroeder M, Helmberger T, Voltz R. Antibody-positive paraneoplastic neurologic syndromes: value of CT and PET for tumor diagnosis. *Neurology* 2004; **63**: 282–286.
14. Younes-Mhenni S, Janier MF, Cinotti L, *et al.* FDG-PET improves tumour detection in patients with paraneoplastic neurological syndromes. *Brain* 2004; **127**: 2331–2338.
15. Horwich MS, Cho L, Porro RS, Posner JB. Subacute sensory neuropathy: a remote effect of carcinoma. *Annals of Neurology* 1977; **2**: 7–19.
16. Graus F, Bonaventura I, Uchya M, *et al.* Indolent anti-Hu-associated paraneoplastic sensory neuropathy. *Neurology* 1994; **44**: 2258–2261.
17. Camdessanche JP, Antoine JC, Honnorat J, *et al.* Paraneoplastic peripheral neuropathy associated with anti-Hu antibodies. A clinical and electrophysiological study of 20 patients. *Brain* 2002; **125**: 166–175.
18. Younger DS, Dalmau J, Inghirami G, *et al.* Anti-Hu-associated peripheral nerve and muscle microvasculitis. *Neurology* 1994; **44**: 181–183.
19. Molinuevo JL, Graus F, Serrano C, *et al.* Utility of anti-Hu antibodies in the diagnosis of paraneoplastic sensory neuropathy. *Annals of Neurology* 1998; **4**: 976–980.

20. Antoine JC, Honnorat J, Camdessanche JP, *et al.* Paraneoplastic anti-CV2 antibodies react with peripheral nerve and are associated with a mixed axonal and demyelinating peripheral neuropathy. *Annals of Neurology* 2001; **49**: 214–221.
21. Honnorat J, Antoine JC, Derrington E, *et al.* Antibodies to a subpopulation of glial cells and a 66 kDa developmental protein in patients with paraneoplastic neurological syndromes. *Journal of Neurology, Neurosurgery and Psychiatry* 1996; **61**: 270–278.
22. Keime-Guibert F, Graus F, Fleury A, *et al.* Treatment of paraneoplastic neurological syndromes with antineuronal antibodies (anti-Hu, anti-Yo) with a combination of immunoglobulins, cyclophosphamide, and methylprednisolone. *Journal of Neurology, Neurosurgery and Psychiatry* 2000; **68**: 479–482.
23. Peterson K, Rosenblum MK, Kotanides H, Posner JB. Paraneoplastic cerebellar degeneration. I. A clinical analysis of 55 anti-Yo antibody-positive patients. *Neurology* 1992; **42**: 1931–1937.
24. Mason WP, Graus F, Lang B, *et al.* Small-cell lung cancer, paraneoplastic cerebellar degeneration and the Lambert–Eaton myasthenic syndrome. *Brain* 1997; **120**: 1279–1300.
25. Bernal F, Shamsili S, Rojas I, *et al.* Anti-Tr antibodies as markers of paraneoplastic cerebellar degeneration and Hodgkin's disease. *Neurology* 2003; **60**: 230–234.
26. Graus F, Lang B, Pozo-Rosich P, *et al.* P/Q type calcium channel antibodies in paraneoplastic cerebellar degeneration with lung cancer. *Neurology* 2002; **59**: 764–766.
27. Shamsili S, Grefkens J, de Leeuw B, *et al.* Paraneoplastic cerebellar degeneration associated with antineuronal antibodies: analysis of 50 patients. *Brain* 2003; **126**: 1409–1418.
28. Fukuda T, Motomura M, Nakao Y, *et al.* Reduction of P/Q-type calcium channels in the postmortem cerebellum of paraneoplastic cerebellar degeneration with Lambert–Eaton myasthenic syndrome. *Annals of Neurology* 2003; **53**: 21–28.
29. 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. *Journal of Neuro-Oncology* 2003; **63**: 187–190.
30. Vernino S, O'Neill BP, Marks RS, *et al.* Immunomodulatory treatment trial for paraneoplastic neurological disorders. *Neuro-oncol* 2004; **6**: 55–62.
31. Rojas I, Graus F, Keime-Guibert F, *et al.* Long-term clinical outcome of paraneoplastic cerebellar degeneration and anti-Yo antibodies. *Neurology* 2000; **55**: 713–715.
32. Anderson NE, Budde-Steffen C, Rosenblum MK, *et al.* Opsoclonus, myoclonus, ataxia, and encephalopathy in adults with cancer: a distinct paraneoplastic syndrome. *Medicine* 1988; **67**: 100–109.
33. Buttner U, Straube A, Handke V. Opsoclonus and ocular flutter. *Nervenarzt* 1997; **68**: 633–637.
34. Straube A, Leigh RJ, Bronstein A, *et al.* EFNS task force-therapy of nystagmus and oscillopsia. *European Journal of Neurology* 2004; **11**: 83–89.
35. Dropcho EJ, Kline LB, Riser J. Antineuronal (anti-Ri) antibodies in a patient with steroid-responsive opsoclonus-myoclonus. *Neurology* 1993; **43**: 207–211.
36. Mitchell WG, Davalos-Gonzalez Y, Brumm VL, *et al.* Opsoclonus-ataxia caused by childhood neuroblastoma: developmental and neurologic sequelae. *Pediatrics* 2002; **109**: 86–98.
37. Gambini C, Conte M, Bernini G, *et al.* Neuroblastic tumors associated with opsoclonus-myoclonus syndrome: histological, immunohistochemical and molecular features of 15 Italian cases. *Virchows Archiv* 2003; **442**: 555–562.
38. Bataller L, Graus F, Saiz A, Vilchez JJ. Clinical outcome in adult onset idiopathic or paraneoplastic opsoclonus-myoclonus. *Brain* 2001; **124**: 437–443.
39. Voltz R. Paraneoplastic neurological syndromes: an update on diagnosis, pathogenesis, and therapy. *Lancet Neurology* 2002; **1**: 294–305.
40. Darnell JC, Posner JB. Paraneoplastic syndromes involving the nervous system. *New England Journal of Medicine* 2003; **349**: 1543–1554.
41. Berger JR, Mehari E. Paraneoplastic opsoclonus-myoclonus secondary to malignant melanoma. *Journal of Neuro-Oncology* 1999; **41**: 43–45.
42. Zamecnik J, Cerny R, Bartos A, *et al.* Paraneoplastic opsoclonus-myoclonus syndrome associated with malignant fibrous histiocytoma: neuropathological findings. *Ceskoslovenska Patologie* 2004; **40**: 63–67.
43. Antunes NL, Khakoo Y, Matthay KK, *et al.* Antineuronal antibodies in patients with neuroblastoma and paraneoplastic opsoclonus-myoclonus. *Journal of Pediatric Hematology/Oncology* 2000; **22**: 315–320.
44. Pranzatelli MR, Tate ED, Wheeler A, *et al.* Screening for autoantibodies in children with opsoclonus-myoclonus-ataxia. *Pediatric Neurology* 2002; **27**: 384–387.
45. Bataller L, Rosenfeld MR, Graus F, *et al.* Autoantigen diversity in the opsoclonus-myoclonus syndrome. *Annals of Neurology* 2003; **53**: 347–353.
46. Prestigiacomo CJ, Balmaceda C, Dalmau J. Anti-Ri-associated paraneoplastic opsoclonus-ataxia syndrome in a man with transitional cell carcinoma. *Cancer* 2001; **91**: 1423–1428.
47. Wong AM, Musallam S, Tomlinson RD, *et al.* Opsoclonus in three dimensions: oculographic, neuropathologic and modelling correlates. *Journal of the Neurological Sciences* 2001; **189**: 71–81.
48. Wirtz PW, Sillevs Smitt PA, Hoff JI, *et al.* Anti-Ri antibody positive opsoclonus-myoclonus in a male patient with breast carcinoma. *Journal of Neurology* 2002; **249**: 1710–1712.
49. Swart JF, de Kraker J, van der Lely N. Meta-iodobenzylguanidine total-body scintigraphy required for revealing occult neuroblastoma in opsoclonus-myoclonus syndrome. *European Journal of Pediatrics* 2002; **161**: 255–258.
50. Hayward K, Jeremy RJ, Jenkins S, *et al.* Long-term neurobehavioral outcomes in children with neuroblastoma and opsoclonus-myoclonus-ataxia syndrome: relationship to MRI findings and anti-neuronal antibodies. *Journal of Pediatrics* 2001; **139**: 552–559.
51. Rudnick E, Khakoo Y, Antunes NL, *et al.* Opsoclonus-myoclonus-ataxia syndrome in neuroblastoma: clinical outcome and antineuronal antibodies—a report from the Children's Cancer Group Study. *Medical and Pediatric Oncology* 2001; **36**: 612–622.
52. Jongen JL, Moll WJ, Sillevs Smitt PA, *et al.* Anti-Ri positive opsoclonus-myoclonus-ataxia in ovarian duct cancer. *Journal of Neurology* 1988; **245**: 691–692.
53. Nitschke M, Hochberg F, Dropcho E. Improvement of paraneoplastic opsoclonus-myoclonus after protein A

- column therapy. *New England Journal of Medicine* 1995; **332**: 192.
54. Wirtz PW, Sotodeh M, Nijhuis M, *et al.* Difference in distribution of muscle weakness between myasthenia gravis and the Lambert–Eaton myasthenic syndrome. *Journal of Neurology, Neurosurgery and Psychiatry* 2002; **73**: 766–768.
 55. O’Neill JH, Murray NM, Newsom-Davis J. The Lambert–Eaton myasthenic syndrome. A review of 50 cases. *Brain* 1988; **111**: 577–596.
 56. Motomura M, Johnston I, Lang B, *et al.* An improved diagnostic assay for Lambert–Eaton myasthenic syndrome. *Journal of Neurology, Neurosurgery and Psychiatry* 1995; **58**: 85–87.
 57. Wirtz PW, Willcox N, van der Slik AR, *et al.* HLA and smoking in prediction and prognosis of small cell lung cancer in autoimmune Lambert–Eaton myasthenic syndrome. *Journal of Neuroimmunology* 2005; **159**: 230–237.
 58. Chalk CH, Murray NM, Newsom-Davis J, O’Neill JH, Spiro SG. Response of the Lambert–Eaton myasthenic syndrome to treatment of associated small-cell lung carcinoma. *Neurology* 1990; **40**: 1552–1556.
 59. Maddison P, Newsom-Davis J, Mills KR, Souhami RL. Favourable prognosis in Lambert–Eaton myasthenic syndrome and small-cell lung carcinoma. *Lancet* 1999; **353**: 117–118.
 60. McEvoy KM, Windebank AJ, Daube JR, Low PA. 3,4-Diaminopyridine in the treatment of Lambert–Eaton myasthenic syndrome. *New England Journal of Medicine* 1989; **321**: 1567–1571.
 61. Hart IK, Waters C, Vincent A, *et al.* Autoantibodies detected to expressed potassium channels are implicated in neuromyotonia. *Annals of Neurology* 1997; **41**: 238–246.
 62. Hart IK, Maddison P, Newsom-Davis J, *et al.* Phenotypic variants of peripheral nerve hyperexcitability. *Brain* 2002; **125**: 1887–1895.
 63. Caress JB, Abend WK, Preston DC, Logigian EL. A case of Hodgkin’s lymphoma producing neuromyotonia. *Neurology* 1997; **49**: 258–259.
 64. Lahrmann H, Albrecht G, Drlicek M, *et al.* Acquired neuromyotonia and peripheral neuropathy in a patient with Hodgkin’s disease. *Muscle and Nerve* 2001; **24**: 834–838.
 65. Zifko U, Drlicek M, Machacek E, *et al.* Syndrome of continuous muscle fiber activity and plasmacytoma with IgM paraproteinemia. *Neurology* 1994; **44**: 560–561.
 66. Newsom-Davis J, Mills KR. Immunological associations of acquired neuromyotonia (Isaacs’ syndrome). Report of five cases and literature review. *Brain* 1993; **116**: 453–469.
 67. Toepfer M, Schroeder M, Unger JM, *et al.* Neuromyotonia, myoclonus, sensory neuropathy and cerebellar symptoms in a patient with antibodies to neuronal nucleoproteins (anti-Hu-antibodies). *Clinical Neurology and Neurosurgery* 1999; **101**: 207–209.
 68. Hayat GR, Kulkantrakorn K, Campbell WW, Giuliani MJ. Neuromyotonia: autoimmune pathogenesis and response to immune modulating therapy. *Journal of the Neurological Sciences* 2000; **181**: 38–43.
 69. Shillito P, Molenaar PC, Vincent A, *et al.* Acquired neuromyotonia: Evidence for autoantibodies directed against K⁺ channels of peripheral nerves. *Annals of Neurology* 1995; **38**: 714–722.
 70. Alessi G, De Reuck J, De Bleecker J, Vancayzeele S. Successful immunoglobulin treatment in a patient with neuromyotonia. *Clinical Neurology and Neurosurgery* 2000; **102**: 173–175.
 71. Ishii A, Hayashi A, Ohkoshi N, *et al.* Clinical evaluation of plasma exchange and high dose intravenous immunoglobulin in a patient with Isaacs’ syndrome. *Journal of Neurology, Neurosurgery, and Psychiatry* 1994; **57**: 840–842.
 72. van den Berg JS, van Engelen BG, Boerman RH, de Baets MH. Acquired neuromyotonia: superiority of plasma exchange over high-dose intravenous human immunoglobulin. *Journal of Neurology* 1999; **246**: 623–625.
 73. Nakatsuji Y, Kaido M, Sugai F, *et al.* Isaacs’ syndrome successfully treated by immunoabsorption plasmapheresis. *Acta Neurologica Scandinavica* 2000; **102**: 271–273.