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

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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 (PNH) (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...
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 en-
hance with contrast injection [5]. In the absence of MRI
abnormalities, FDG-PET studies should show an in-
creased 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.

Onconeuronal antibodies may be found in the serum
and CSF of about 60% of patients with PLE. The most
frequent onconeuronal antibodies are anti-Hu, anti-
Ma2 (with or without anti-Ma1), anti-CV2/CRMP5
and anti-amphiphysin. Seventy-eight per cent of pa-
tients with PLE and anti-Hu have symptoms that sug-
gest a dysfunction in areas of the nervous system other
than the limbic system. In fact, PLE may be the pre-
senting 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 dys-
function. 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 anti-
bodies 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 de-
tect SCLC include high resolution computed tomogra-
phy (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. Bronchos-
copy 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 tes-
ticular 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 symp-
toms.

Subacute sensory neuronopathy

Clinical features

Several neuropathies have been reported as paraneo-
plastic, 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 med-
ian delay of 4.5 months [12]. The onset of SSN is usu-
ally 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
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 mononeuropathy 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 pancebellar 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 opscoclonus-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 adrenocorticotropic 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, impained 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.
References


