Paraneoplastic Neurological Syndromes

27

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Key Facts

- **Terminology and definition** – Diseases of the nervous system generated by the remote, nonmetastatic effect of a malignancy.
- **Clinical features** – Acute/subacute onset of focal or multifocal involvement of central, peripheral, and autonomic nervous system.
- **Diagnostic markers**
  - **Laboratory**
    - CSF with increased lymphocytes and protein, IgG intrathecal synthesis. Positivity for onconeural and neuronal surface antibodies in serum and CSF.
  - **Pathology** (variable, depending on Ab association); IgG and complement deposits, gliosis, neuronal loss, B cells and plasma cell infiltrates.
- **Top differential diagnosis** – Prion disease, infectious encephalitis, degenerative disorders, temporal lobe epilepsy, toxic and metabolic ataxia, radiculopathies, vitamin B12 deficiency, Guillain-Barré syndrome.
- **Therapy** – Steroids and immunoglobulins are efficacious in children affected by opsoclonus-myoclonus. Plasma exchange, steroids, and intravenous immunoglobulins can be very effective in *PNS associated with antibodies against surface antigens*.
- **Prognosis** – The prognosis of individual paraneoplastic neurological diseases varies considerably. In forms involving antibodies against neuronal surface antigens, tumor removal and immunosuppressive treatment can lead to complete recovery. Two years after onset, 50 % of patients with paraneoplastic encephalomyelitis, limbic encephalitis, and dysautonomia had died. Patients with sensory neuronopathy, paraneoplastic cerebellar degeneration, and Lambert-Eaton syndrome had a better prognosis, with over 50 % of patients surviving at 24 months.

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Abbreviations

ADH, antidiuretic hormone; CSF, cerebrospinal fluid; EMG, electromyography; LE, Limbic Encephalitis; LEMS, Lambert-Eaton myasthenic syndrome; OMS, Opsoclonus-myoclonus syndrome; OMS, opsoclonus-myoclonus syndrome; PCD, paraneoplastic cerebellar degeneration; PEM, paraneoplastic encephalomyelitis; PNS, paraneoplastic neurological syndromes; SCLC, small-cell lung cancer; SPS, Stiff Person Syndrome; SSN, sensory neuronopathy

27.1 Terminology and Definitions

Paraneoplastic neurological syndromes (PNS) are a group of diseases caused by nervous system impairment generated by the non-metastatic remote effect of a malignancy.

27.2 Clinical Features

Approximately one in 10,000 patients with a tumor can develop a symptomatic PNS [1]. Some forms occur more frequently, as Lambert-Eaton disease (3 % of patients affected by small-cell lung cancer [SCLC]) [2]; 50 % of patients with osteosclerotic plasmacytoma are affected by POEMS syndrome, and a growing number of cases of encephalitis associated with anti-NMDA receptor and VGKC antibodies are being reported.

The clinical characteristics of individual PNS vary according to the site involved. Nonetheless, it is helpful to specify two common characteristics:

(a) The neurological signs and symptoms have a subacute onset
(b) The neurological disease often precedes clinical evidence of the tumor

27.2.1 Classification According to Associated A ntibodies

The pathogenesis of PNS is immune mediated. The immune response causing the disease produces various types of antibodies directed against antigens located in the central or peripheral nervous system. PNS can be classified into two categories.

1. PNS associated with antibodies directed against intraneuronal antigens ectopically expressed by the tumor cells (onconeural antibodies). They accompany cancers (lung, breast, ovary, and testicular) and are characterized by poor responsiveness to tumor removal and immunomodulatory or immunosuppressive therapy. The antibodies associated with this group of PNS do not have pathogenic relevance, but are highly specific diagnostic markers.
2. The PNS associated with antibodies directed against neuronal surface antigens (e.g., NMDA- or AMPA-type glutamate receptor proteins associated with potassium channels, such as LGI1 or CASPR2, etc.) are less frequently associated with an underlying tumor but can be paraneoplastic and associated with teratomas, thymomas, and SCLC. This group differs in its greater responsiveness to treatment and typically manifests in forms of encephalitis and encephalopathy; peripheral forms have also been described: neuromyotonia and Lambert-Eaton myasthenic syndrome (LEMS).

27.2.2 Paraneoplastic Encephalomyelitis

Paraneoplastic encephalomyelitis (PEM) constitutes the paradigm of PNS. Pathologically, it is characterized by neuronal loss, microglial

proliferation, and inflammatory infiltrates with multifocal distribution. Its multiregional clinical picture can affect the hippocampus, trunk, spinal cord, or dorsal root ganglia. Involvement can also extend to the peripheral nerves and myenteric plexus, giving rise to encephalomyeloneuritis.

27.2.3 Paraneoplastic Cerebellar Degeneration

Paraneoplastic cerebellar degeneration (PCD) has a subacute course. Its progression often confines the patient to bed within 3 months, although symptoms can subsequently stabilize. PCD is associated with ovarian and breast cancer, SCLC, and Hodgkin's lymphoma.

27.2.4 Sensory Neuronopathy (See Chap. 27)

Sensory neuronopathy (SSN) involves the neuronal cell body in the dorsal root ganglion. It is associated with SCLC in 70–80 % of cases, but can also present during ovarian or breast cancer, sarcoma, or Hodgkin's lymphoma. The onset of SSN is subacute and rapidly progressive, stabilizing after a few weeks.

The pathological process leads to a typical asymmetric, non-length-dependent pattern of sensory nerve degeneration. Symptoms include dysesthesia and mainly deep sensory loss, with sensory ataxia. SSN affects 74 % of patients with paraneoplastic encephalomyelitis.

SSN is prevalently associated with anti-Hu antibodies.

27.2.5 Opsoclonus-Myoclonus Syndrome

Opsoclonus-myoclonus syndrome (OMS) is characterized by chaotic saccadic eye movements in all gaze directions, and is associated with ataxia and head, trunk, and limb myoclonus. Paraneoplastic forms of OMS are relatively rare, whereas idiopathic forms are more often observed in children affected by neuroblastoma or in women with breast cancer harboring anti-Ri antibodies.

27.2.6 Paraneoplastic Limbic Encephalitis Associated with Onconeural Antibodies

Paraneoplastic limbic encephalitis (PLE) is characterized by the classic triad of anterograde amnesia, seizures, and psychiatric symptoms. PLE precedes clinical evidence of malignancy by up to 4 years. Onset is acute or subacute. Seizures are present in approximately 50 % of patients [3]. Extra-limbic symptoms may also be present with sleep disorders and dysautonomia.

27.2.7 Encephalitis with Anti-VGKC Antibodies (Anti-LGI1 and Anti-CASPR2)

Anti-VGKC antibody-associated limbic encephalitis differs from classical PLE in its good response to immunomodulatory therapy and in its high proportion of nonparaneoplastic cases (up to 70–80 %). Characteristic is the frequent presence of refractory hyponatremia due to inappropriate antidiuretic hormone (ADH) syndrome.

Anti-VGKC-Ab may be specific for leucine-rich glioma inactivated protein 1 (LGI1) and contactin-associated protein-2 (CASPR2), associated with VGKC channels. Patients with anti-LGI1 antibodies present typical forms of limbic encephalitis, while those harboring anti-CASPR2 antibodies present encephalitis-like symptoms (cognitive deficits, confusion, amnestic disorders, hallucinations, seizures) associated with peripheral hyperexcitability (Morvan's syndrome) [4].

27.2.8 Encephalitis with ANTI-NMDA-Receptor Antibodies

Anti-NMDAR receptor encephalitis is probably the most frequent form of encephalitis associated with antibodies directed against surface antigens. It more frequently affects females (70–80 % of cases) of a mean age of 22–23 years and children (up to 40 % of cases).

In 70 % of cases, patients experience onset with prodromal flu-like symptoms, followed a few days later by typical manifestations of the pathology, consisting of:

(a) Psychiatric symptoms
(b) Cognitive disorders
(c) Depressed consciousness
(d) Movement disorders (orofacial dyskinesias, dystonia)
(e) Seizures
(f) Dysautonomia
(g) Hypoventilation

While the primary signs in adults are chiefly psychiatric, children more often manifest movement disorders and seizures.

27.3 Diagnostic Markers

CSF Signs of inflammation, oligoclonal bands.

Brain MRI Inflammatory lesions in the temporal region (limbic encephalitis/LE, Fig. 27.1), cerebellar atrophy (PCD).

EEG Non-specific slow disorganized or epileptic activity.

Electromyography (EMG) Non-length dependent pattern (SSN); decremental response to repetitive nerve stimulation (myasthenia) and post-tetanic potentiation of CMAP (LEMS), peripheral hyperexcitability with fibrillation, and fasciculations (neuromyotonia).

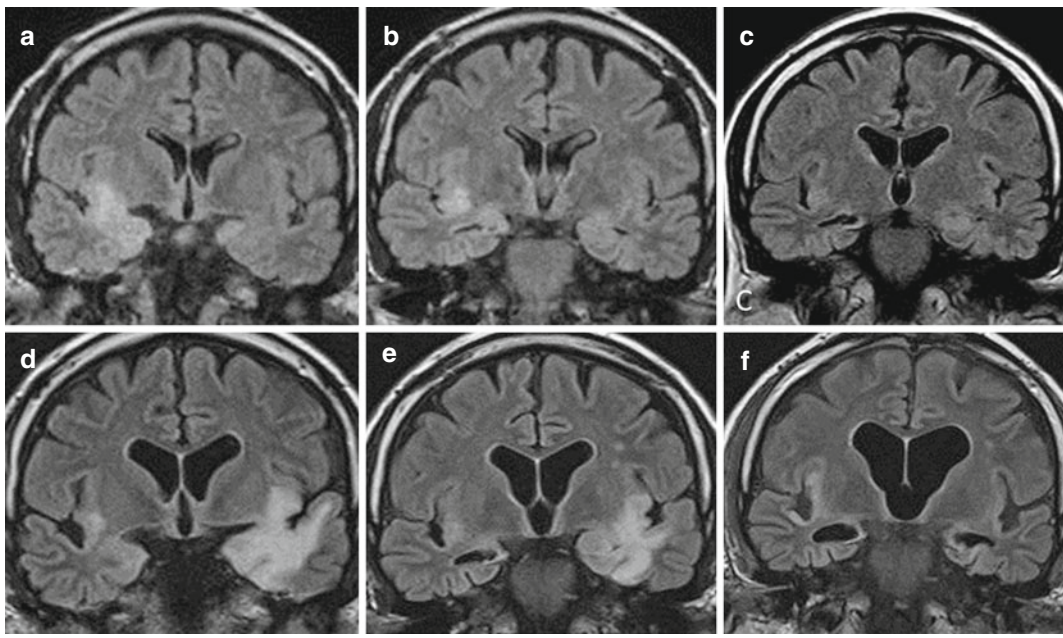

Fig. 27.1 Paraneoplastic limbic encephalitis. Coronal Flair images. (**a**, **b**) demonstrate first acute phase with swelling and hyperintensity in right insular and mesial temporal lobes; after 3 months, (**c**) atrophy is clearly observed. In (**d**, **e**) a second acute phase with swelling and hyperintensity is seen in the left temporal mesial and partially in the insular lobes. After 3 months, (**f**) bilateral marked hippocampal atrophy is present

Table 27.1 Onconeural antibodies: association with tumors and PNS

Antibody	Most commonly associated tumors	Syndrome	Antibody positivity without a tumor (%)	Frequency in tumor without PNS (%)
Anti-Hu	SCLC	Encephalomyelitis Limbic encephalitis PCD Brainstem encephalitis Intestinal pseudo-obstruction	2	16
Anti-CV2	SCLC, thymoma	Encephalomyelitis Chorea PCD Limbic encephalitis	4	9
Anti-amphiphysin	Breast, SCLC	SPS Myelopathy PEM	5	1
Anti-Ri	Breast, SCLC	Brainstem encephalitis Opsoclonus-Myoclonus	3	4
Anti-Yo	Ovary, breast	PCD	2	1
Anti-Ma2	Testicle	Limbic encephalitis Brainstem encephalitis	4	0

Table 27.2 Antibodies against surface antigens: most common association with tumors and syndromes

Antibody	Syndromes	Most commonly associated tumors	Frequency of paraneoplastic cases
Anti-LGI1	Limbic encephalitis	SCLC, thymoma	Rare
Anti-Caspr2	Limbic encephalitis, neuromyotonia, Morvan's syndrome	Thymoma	40 %
Anti-NMDAR	Encephalitis	Ovarian teratoma	6 % in children; 50 % in adults
Anti-AMPAR	Limbic encephalitis	SCLC, breast, thymoma	70 %
Anti-GABAR	Limbic encephalitis	SCLC	50 %
Anti-VGCC	LEMS	SCLC	50–60 %

Antibody Screening The antibodies are associated with clinical syndromes and tumors according to a number of common patterns (see Tables 27.1 and 27.2).

Onconeural antibodies can be detected in serum and CSF, with high concordance of results.

Tumor Screening (see Tables 27.1 and 27.2) – The search for specific tumors is guided by the clinical manifestation and, above all, the type of autoantibody [5]. In the case of limbic encephalitis, for instance, the target of cancer screening is possibly a SCLC, but also a thymoma. More rarely associated malignancies include ovarian, renal, and uterus tumors, Hodgkin's lymphoma, breast and testicular cancer, and neuroblastoma in children. Screening in cerebellar degeneration focuses on the detection of lymphoma, ovarian, breast, and lung cancers.

Opsoclonus-myoclonus: neuroblastoma, lung cancer. Lambert-Eaton: SCLC.

If oncological screening is negative, it is recommended to repeat the tests at 6-month intervals for a period of up to 4 years. This indication applies particularly to cases associated with onconeural antibodies, since the absence of a tumor is very rare in such cases.

If CT and MRI are negative, a total body PET scan should be performed.

27.4 Differential Diagnosis

In the workup of patients with suspected PNS, the differential diagnosis rules out causes producing similar clinical pictures such as, in the case of limbic encephalitis, viral encephalitis (Herpes simplex virus, HHV-6), Creutzfeldt-Jacob

disease, rapidly progressive dementia, or temporal glioma. Infectious, post-infectious, toxic, metabolic, deficiency-induced cerebellitis in the case of PCD and radiculopathy, vit. B12 deficiency, Guillain-Barré syndrome, CIDP, amyloid, hereditary, vasculitic neuropathy in case of SSN.

27.5 Prognosis

27.5.1 Principles of Treatment

Therapeutic strategies are designed to treat the cancer and control the immune response with immune modulation or immunosuppressive treatments.

27.5.1.1 Treatment of PNS Associated with Onconeural Antibodies

The efficacy of immunotherapy with steroids, plasma exchange, and intravenous immunoglobulins is very modest. The use of steroids and immunoglobulins has produced some results in children affected by opsoclonus-myoclonus. Anti-Ma2-antibody-associated encephalitis also appears to respond to treatment with high dose steroids.

The T-cell mediated mechanisms of many PNS, prompt immunosuppressive treatment with drugs such as cyclophosphamide, tacrolimus or mycophenolate mofetil, particularly in cases with worsening neurological signs and in patients with moderate-low disability (Rankin < 4).

Although immunosuppression can theoretically stimulate tumor progression, there has been no demonstration that immunosuppression is negatively correlated with the survival prognosis [6].

27.5.1.2 Treatment of PNS Associated with Antibodies Against Surface Antigens

Plasma exchange, steroids and intravenous immunoglobulins, followed or accompanied by immunosuppressive drugs can be very effective.

If first-line immunomodulation fails in forms that tend to be monophasic (but are inclined to relapse), as in anti-NMDA receptor encephalitis, it is common practice to start immunosuppressive treatment with cyclophosphamide (750 mg/m^2 per month) and/or rituximab until a clinical response is achieved. Once the acute phase is over, particularly in non-paraneoplastic cases, maintenance immunosuppression (e.g., with azathioprine or mycophenolate mofetil) for at least 1 year is an option that seems to reduce the risk of relapse [7].

27.5.2 Disability

There is undoubtedly a high degree of disability among patients with PNS since the rapid evolution of the pathology and the neuropathological mechanism of neuronal destruction mean that the best result treatment can offer is rapid control of the malignancy, which may help stabilize the neurological picture. Only symptomatic treatment approaches can slightly attenuate symptoms or slightly improve mobility.

The scenario changes in forms involving antibodies against neuronal surface antigens since tumor removal or early immunosuppressive treatment can lead to total symptom remission and thus complete recovery from the disease.

However, there are conditions, such as encephalitis associated with LGI1, in which 20–30 % of cases do not respond to treatment or forms associated with AMPAR and GABAb. These patients may present residual drug-resistant seizures and require continuous adjustments to the pharmacological therapy.

Lastly, there is a 20 % risk of recurrence in patients with anti-NMDA-receptor encephalitis and in patients with LGI1 antibodies. The recommendation in these cases is to slowly and gradually suspend immunosuppressive treatment and, in the case of recurrence, to consider the option of second-line immunosuppression.

27.5.3 Prognosis

Oncologically, however, it has been demonstrated that in the presence of paraneoplastic neurological disease, the tumor has a much less aggressive

course and therefore a better prognosis. Only rarely does the tumor present distant metastases, tending to remain localized or to invade solely into the regional lymph nodes. Ninety percent of these patients present limited oncological disease at the time of diagnosis compared to 50–60 % of patients with breast cancer and 25 % with an ovarian tumor.

Analysis of European database data has confirmed that two-thirds of patients with paraneoplastic disease presented no evidence of malignancy at the time of neurological diagnosis. Diagnosis was the result of careful, targeted diagnostic work-up and in many cases came after 3 years of follow up. The neurologist is, therefore, the first specialist with whom these patients should come into contact.

The prognosis of individual paraneoplastic neurological diseases varies considerably. Data from the said database have revealed that 2 years after onset of the neurological disease, over 50 % of patients with paraneoplastic encephalomyelitis, limbic encephalitis, and dysautonomia had died, in the majority of cases due to progression of the neurological disease. Conversely, patients with sensory neuronopathy, paraneoplastic cerebellar degeneration, and Lambert-Eaton syndrome (see Chap. 25) had a better prognosis, with over 50 % of patients surviving at 24 months, despite the presence of comparable oncological diseases in the two groups.

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