Paraneoplastic Neurological Syndromes

16

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Key Points

1. Paraneoplastic neurological syndromes (PNS) can affect any part of the nervous system. Classical PNS include limbic encephalitis, cerebellar degeneration, opsoclonus-myoclonus syndrome, encephalomyelitis, sensory neuropathy, and Lambert-Eaton myasthenic syndrome (LEMS).
2. PNS occur in association with cancer; however, they are not due to cancer invasion or complication of its treatment, but rather to the immune response directed against proteins shared between tumor cells and neurons.
3. PNS are characterized by the detection in the serum and cerebrospinal fluid (CSF) of antibodies reacting with neuronal intracellular antigens (e.g., Hu or Yo). Neuronal dysfunction is not caused by these antibodies, which are considered as markers of the underlying tumor, but is due to T-cell cytotoxicity.
4. The diagnosis of PNS relies on recognition of the clinical syndrome and detection of the associated cancer and autoantibodies in serum and CSF.
5. Response of PNS to tumor treatment and immunotherapy is generally poor.

Introduction

Paraneoplastic neurological syndromes (PNS) are immune-mediated disorders that can affect any part of the neuraxis, from the central nervous system (CNS), including the retina, to peripheral nerves and neuromuscular junction. PNS can manifest with a variety of neurological symptoms, which can derive from dysfunction of one area of the nervous system (e.g., limbic encephalitis or brainstem encephalitis), single cell population (e.g., Purkinje cells in paraneoplastic cerebellar degeneration or ganglionic cells in paraneoplastic retinopathy), or multiple areas (e.g., encephalomyelitis).

These disorders occur in association with cancer; however, they are not due to cancer invasion or complication of its treatment, but rather to the immune response directed against proteins shared between tumor cells and neurons, which causes neuronal dysfunction or damage. Importantly, the onset of neurological symptoms often precedes (or leads to) the diagnosis of cancer by months or

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even years. Thus, considering also that in most cases the underlying cancer is of small size and limited stage, detection of PNS represents an opportunity for early cancer diagnosis and treatment.

PNS are rare disorders that occur in 1 out of 10,000 patients with cancer, with the exception of some PNS affecting the neuromuscular junction, such as Lambert-Eaton myasthenic syndrome (LEMS), which can be much more common [1]. Not all cancer types have the same propensity to trigger PNS; some, such as small-cell lung cancer (SCLC), breast and gynecologic cancers, and non-solid tumors (in particular Hodgkin's lymphoma), are more frequently associated with PNS than others.

PNS are characterized by the detection in the serum and cerebrospinal fluid (CSF) of antibodies reacting with neuronal antigens, which are also expressed by tumor cells. These antibodies are also called onconeuronal because of their relation to PNS and cancer. Some onconeuronal antibodies are associated with a specific neurological syndrome, for instance, Yo antibodies with paraneoplastic cerebellar degeneration [2] and Ma2 antibodies with limbic or brainstem encephalitis [3], whereas others can be associated with a wider range of neurological manifestations, such as Hu antibodies, which can be found in patients with paraneoplastic limbic encephalitis, neuronopathy, encephalomyelitis, or others [4, 5].

This chapter focuses on the main PNS involving the CNS; those affecting the peripheral nervous system and neuromuscular junction will be discussed in separate sections (Part 4: Chaps. 18, 19, 20, and 21). This chapter aims to (1) facilitate recognition and diagnosis of these disorders by providing clinical features, CSF analysis, magnetic resonance imaging (MRI) findings, and tumor association, exemplified by two clinical cases; (2) describe the associated onconeuronal antibodies and discuss their role in the pathogenesis of neuronal damage; and (3) summarize the therapeutic approach (discussed in detail in Chap. 17) and response of neurological symptoms to tumor treatment and immunotherapy.

Clinical Cases

Clinical Case 1

A 59-year-old woman was referred for a 1-month history of diplopia and vertigo, followed by progressive development of gait instability, limb incoordination, and speech difficulties. Neurological symptoms progressed over the following weeks to severe ataxia with inability to stand, walk, or eat unassisted. Neurological examination showed a severe pancerebellar syndrome with trunk, limb, and gait ataxia, downbeat nystagmus, and dysarthria. Brain MRI was unremarkable. CSF analysis showed no pleocytosis but elevated immunoglobulin G (IgG) index and protein. Oncologic screening revealed breast cancer with axillary lymph node involvement. Antibodies against Yo were found at high titers in serum and CSF, confirming the diagnosis of Yo antibody-associated paraneoplastic cerebellar degeneration. Cancer treatment, including surgery, chemotherapy, and radiotherapy, followed by immunotherapy with corticoids and rituximab, resulted in neurological stabilization. At 15 months from onset, because of neurological worsening, rituximab was changed to mycophenolate mofetil without further progression of her cerebellar syndrome. Brain MRI at 26 months from onset showed diffuse cerebellar atrophy (Fig. 16.1). At the last follow-up, 3.5 years from onset, the patient was clinically stable, with no evidence of tumor relapse.

Clinical Case 2

A 52-year-old woman, current smoker, presented with gradual onset of sensory disturbances in her hands and feet, including numbness, prickling, and tingling, which progressively spread to the arms and legs. Sensory symptoms were associated with intermittent sharp, throbbing pain, and extreme sensitivity to touch. She also developed limb ataxia and gait instability, especially in poor lighting conditions, and complained of excessive sweating and urinary retention. Neurological

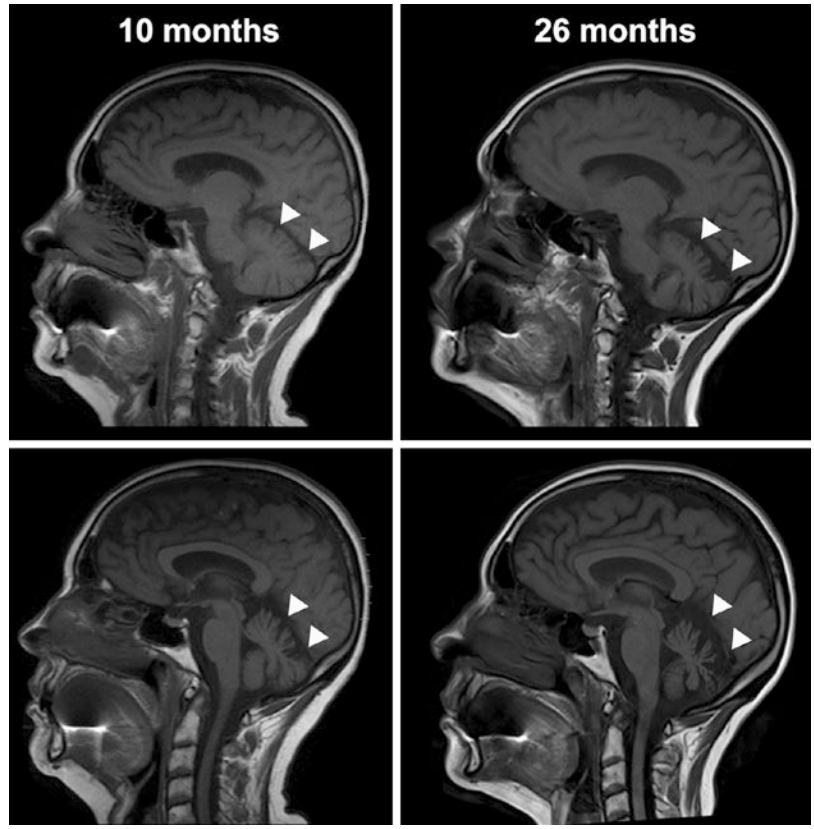

Fig. 16.1 Evolution of cerebellar atrophy at 10 and 26 months from onset in a woman with anti-Yo paraneoplastic cerebellar degeneration (*Clinical Case 1*). Notice the progressive enlargement of the cerebellar interlobular fissures (upper panels, arrow heads) and CSF space under the tentorium cerebelli (lower panels, arrow heads), indicating cerebellar atrophy. (*Courtesy of Dr. Francesc Graus*)

examination revealed alteration of all sensory modalities in the lower limbs and to a lesser extent also the upper limbs, dysdiadochocinesia, severe sensory ataxia with abolished vibratory and position sense, and altered thermoalgesia of the right face. Osteotendinous reflexes were normal in the upper limbs and absent in the lower limbs, plantar reflex was bilaterally flexor. Muscle strength was normal. Nerve conduction studies revealed the absence of sensory nerve responses in the lower limbs and right trigeminal nerve and responses of decreased amplitude in the upper limbs, with normal motor studies. Oncologic screening found oat cell carcinoma of the lung and elevated Hu antibodies in the serum and CSF (Fig. 16.2), confirming the diagnosis of paraneoplastic neuronopathy associated with Hu antibodies. Tumor removal, chemotherapy, and radiotherapy resulted in partial improvement of neurological symptoms and disappearance of Hu antibodies from the serum. After 8 years, the patient progressively developed severe motor weakness and atrophy, which predominated in the lower limbs, obliging her to ambulate in a wheelchair. Hu antibodies reappeared in the serum at high titers, but there was no evidence of tumor relapse. The patient was treated with corticoids without improvement but stabilization of the neurological syndrome.

General Concepts

Diagnosis

The diagnosis of PNS relies on recognition of the clinical syndrome and detection of the associated cancer and onconeuronal antibodies in serum and CSF [6].

When evaluating a patient with suspected PNS, clinicians should carefully consider the patient's age and sex, clinical features (some neurological syndromes, such as limbic encephalitis, being more suggestive of a paraneoplastic origin

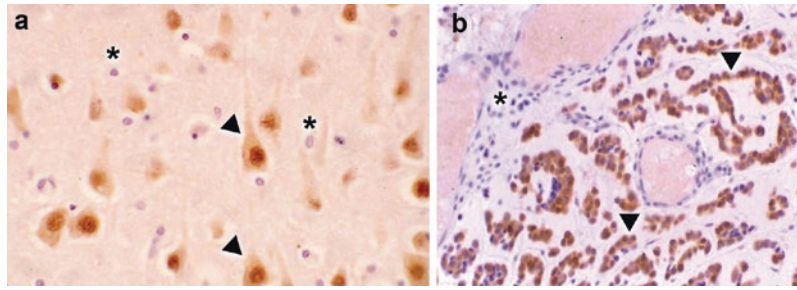

Fig. 16.2 Immunolabeling of rat brain (**a**) by anti-Hu serum from a patient with paraneoplastic encephalomyelitis and breast cancer. Hu antibodies strongly react with the nucleus (and to a lesser extent also with the cytoplasm) of neurons (**a**, arrow heads) but do not label glial cells (**a**, star). These antibodies also react with breast cancer cells (**b**, arrow heads), which express Hu proteins, but do not label the surrounding normal breast tissue (**b**, star). Immunoperoxidase technique, slightly counterstained with hematoxylin; original magnification ×800 and ×200. (*Courtesy of Dr. Francesc Graus*)

than others), cancer risk factor (e.g.., smoking), and previous history of cancer. Findings that support diagnosis of PNS include CSF analysis showing low to moderate lymphocytic pleocytosis, increased IgG index, and oligoclonal bands. Although these findings are not specific to PNS, as they can be found in patients with other inflammatory disorders, CSF analysis is fundamental to rule out other pathologies and cancer complications, such as leptomeningeal carcinomatosis. Brain MRI abnormalities are also usually nonspecific, with the exception of unilateral or bilateral hyperintensities of mesial-temporal lobes in patients with limbic encephalitis. However, both CSF analysis and brain MRI can be completely normal in patients with PNS. In these cases, brain 18F-fluorodeoxyglucose position emission tomography (18F-FDG-PET) can be helpful as it can reveal metabolic abnormalities in brain areas that appear structurally normal by MRI [7]. In patients for whom the diagnosis remains uncertain, biopsy of lesions identified by brain MRI or 18F-FDG-PET might help to exclude other diagnoses or support an immune-mediated process.

Detection of onconeuronal antibodies in the CSF confirms the diagnosis of PNS. However, it is important to underline that the presence of these antibodies only in serum is not confirmatory, as they can be found, most often at low titers, in the serum of patients with cancer and no PNS. Identification of onconeuronal antibodies is also important because it can suggest the most likely underlying tumor. For instance, Ma2 antibodies are highly suggestive of an underlying testicular tumor, whereas identification of Hu antibodies should prompt search of SCLC.

Patients with suspected PNS should undergo careful tumor screening, taking into consideration that the associated tumor might be small in size and difficult to detect. Tumor search should be guided by the clinical syndrome and detected onconeuronal antibody. Some paraneoplastic syndromes (e.g., cerebellar degeneration with Yo antibodies) are so closely associated with a specific tumor type (breast or ovarian cancer) that if the tumor found does not correspond to the typically expected, a second neoplasm should be suspected [8]. Serum oncologic markers such as Ca-125, carcinoembryonic antigen, or prostate-specific antigen can be helpful. Whole-body computed tomography (CT) and 18F-FDG-PET have been suggested to be the best methods to identify occult cancers [9]. Pelvic and testicular tumors are best investigated by ultrasound, whereas mammography is the first choice to identify breast cancer [10]. If no tumor is found, and clinical suspicion of PNS remains high, it is recommended to repeat tumor screening every 6 months for up to 4 years [10], although in the vast majority of the patients the underlying tumor is identified within the first year after PNS onset [11].

Clinical Syndromes

PNS can manifest with a variety of neurological syndromes, and their association with cancer varies according to the detected neuronal antibody. For example, stiff person syndrome (see later) typically occurs in patients without cancer who have antibodies to glutamic acid decarboxylase (GAD65); however, this syndrome can also occur in association with amphiphysin antibodies, which most likely occur in patients with cancer. Overall, neurological syndromes that are most frequently associated with cancer are called *classical PNS*, as opposed to *non-classical PNS*, which can frequently occur in the absence of cancer. It is important to consider that both *classical* and *non-classical PNS* can occur in patients without cancer, but what makes them paraneoplastic is their increased occurrence in patients with cancer. Table 16.1 provides an overview of the main *classical* and *non-classical* PNS and associated onconeuronal antibodies.

Table 16.1 The main paraneoplastic syndromes of the central and peripheral nervous system

Paraneoplastic syndrome	Onconeuronal antibodies
Brain, retina, brainstem, and cerebellum	
Limbic encephalitis[a]	Hu, Ma2, GAD65, AK5
Cerebellar degeneration[a]	Yo, PCA-2, Ri, Tr, Hu
Retinopathy (CAR, MAR), optic neuritis[a]	Recoverin, bipolar ganglionic cells, CV2/CRMP5
Basal ganglia and diencephalon	Hu, Ma2, CV2/CRMP5
Brainstem encephalitis	Ma2, CV2/CRMP5
Opsoclonus-myoclonus syndrome[a]	Ri, Hu, Ma2, amphiphysin, CV2/CRMP5
Spinal cord	
Encephalomyelitis[a]	Hu, CV2/CRMP5, amphiphysin
Amyotrophic lateral sclerosis	CV2/CRMP5, Ma2, Yo, amphiphysin
Inflammatory myelitis	Hu, CV2/CRMP5, GAD65, Ri, PCA-2
Stiff person syndrome	GAD65, amphiphysin, Ri, gephyrin
Dorsal roots, peripheral nerve, and neuromuscular junction	
Sensory neuronopathy[a]	Hu, CV2/CRMP5
Subacute motor neuropathy[a]	Hu
Autonomic neuropathy	Hu, PCA-2
Chronic gastrointestinal pseudo-obstruction[a]	–
Polyradiculopathy (acute or chronic)	CV2/CRMP5
Lambert-Eaton myasthenic syndrome[a]	P/Q VGCC, SOX1

[a]Classical paraneoplastic syndromes

Pathogenesis

The pathogenic mechanisms underlying PNS are not fully understood. It is thought that tumor cells, which express ectopic proteins, can trigger an anti-tumor immune response against these proteins, which are also expressed in neurons. Apoptotic tumor cells might indeed be phagocytosed by dendritic cells, which then present tumor antigens to B and T cells at local lymph nodes (Fig. 16.3) [12]. It is currently believed that PNS are mainly mediated by cytotoxic T-cell responses against intracellular antigens and that onconeuronal antibodies against the same antigens participate to, but are not directly causing, neuronal damage [13–15]. The idea that these antibodies might be implicated in the development of PNS has been suggested by the observation that Hu antibodies, for instance, accumulate inside neurons and they are found at higher concentration in injured brain areas, correlating with the main clinical symptoms [16]. However, several observations and experimental evidence support a minor role of these antibodies: (1) antibody titers do not correlate with neurological symptom severity and may persist despite improvement or resolution of PNS [17]; (2) target antigens, being localized inside the neuron, are not directly accessible to circulating antibodies; (3) patients' Hu antibodies can enter neurons but do not cause neuronal dysfunction/cytotoxicity [18, 19]; and (4) animal models obtained by intrathecal infusion of patients' antibodies or immunization with Hu or Yo recombinant proteins with production of neuronal antibodies have failed to reproduce the human disorder [20, 21]. Overall, all onconeuronal antibodies are thought to be not directly

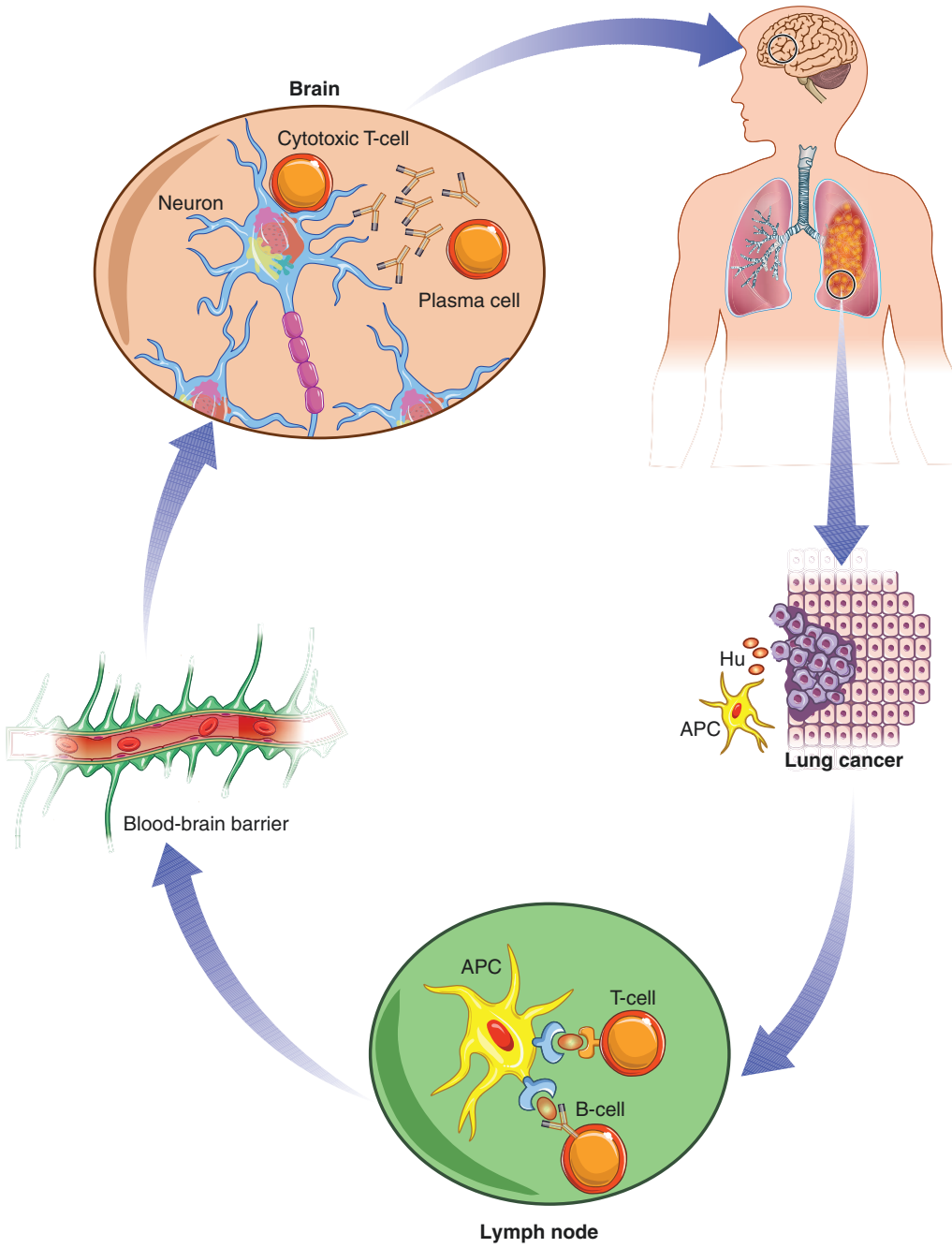

Fig. 16.3 Possible pathogenesis of paraneoplastic neurological syndromes. Neuronal antigens (e.g., Hu), which are ectopically expressed by tumor cells (e.g., small-cell lung cancer) undergoing apoptosis, are uptaken by dendritic cells (antigen-presenting cell or APC). APC then migrates to local lymph nodes and presents these antigens to T cells and B cells. Activated T cells and B cells enter the blood stream, pass the blood-brain barrier, penetrate into the brain parenchyma, and react with neuronal antigens. Although antibody-producing plasma cells participate to the autoimmune response, T cells (in particular cytotoxic CD8+ lymphocytes) are the main responsible for neuronal damage and death

pathogenic, with the exception of those targeting intracellular synaptic proteins, such as amphiphysin. Indeed, there is evidence that these antibodies may have access to their target proteins during synaptic vesicle fusion and thus cause direct neuronal damage (see later).

Therapeutic Approach and Prognosis

Treatment of PNS (discussed in detail in Chap. 17) is based on oncologic therapies, in cancer-associated cases, and can be complemented with immunotherapies, including corticosteroids, intravenous immunoglobulins, plasmapheresis, or immunosuppressive therapy (such as rituximab or cyclophosphamide). The response of neurological symptoms to these therapies is variable and depends on the specific PNS and associated onconeuronal antibody, as shown in Table 16.2 [1, 3, 5, 22–28]. Overall, patients with PNS show poor response to successful tumor treatment and immunotherapies (with some exception, such as GAD65 antibody-associated stiff person syndrome), likely in relation to early irreversible neuronal damage [5, 29]. However, it

Table 16.2 The main onconeuronal antibodies, associated paraneoplastic neurological syndromes and tumor, and response to tumor treatment and immunotherapy

Antibody	Cell-type target	Neurological syndrome	Tumor frequency (% patient) and type	Response to treatment
Nuclear antibodies				
Hu (ANNA-1)	All neuron type of the central and peripheral nervous system	Limbic encephalitis Encephalomyelitis Cerebellar degeneration Sensory neuropathy Autonomic dysfunction	90% [5] Small-cell lung cancer, neuroblastoma, gynecologic, breast, prostate cancer	Poor, some patients show stabilization of neurological symptoms
Ri (ANNA-2)	All neuron type of the central nervous system	Opsoclonus-myoclonus syndrome Brainstem encephalitis Stiff person syndrome	85% [22] Breast, Small-cell and non-small-cell lung cancer, gynecologic, bladder, lymphoma	60% of patients show moderate improvement, some have resolution
Ma1 and Ma2	All neuron type of the central and peripheral nervous system	Limbic encephalitis Diencephalic or brainstem encephalitis	90% [3] Testis (mostly germ cell cancer)	30–50% of patients improve
ZIC4	All neuron type, particularly in the cerebellum	Encephalomyelitis Cerebellar degeneration	95% [23]	Poor
SOX1 (AGNA-1)	Bergman glia, Golgi neurons	LEMS Limbic encephalitis Cerebellar ataxia	90% [1] Small-cell lung cancer	Poor
Cytoplasmic antibodies				
Yo (PCA-1)	Purkinje neurons, deep cerebellar nuclei	Cerebellar degeneration	90% [24] Ovarian cancer, breast cancer, lung cancer	Poor

(continued)

Table 16.2 (continued)

Antibody	Cell-type target	Neurological syndrome	Tumor frequency (% patient) and type	Response to treatment
PCA-2 (MAP1B)	Purkinje neurons	Limbic encephalitis Brainstem encephalitis Cerebellar degeneration LEMS Autonomic neuropathy	80% [25] Small-cell lung cancer	Poor
Tr (PCA-Tr or DNER)	Purkinje neurons	Cerebellar degeneration	90% [26] Hodgkin's lymphoma	20% of patients respond
CV2 (CRMP5)	Oligodendrocytes ≫ neurons of the cortex, cerebellum, and optic nerve	Encephalomyelitis Cerebellar degeneration Chorea Sensory neuropathy Retinopathy, optic neuropathy	90% [27] Small-cell lung cancer (60%), malignant thymoma, uterine sarcoma	Some patients respond with substantial improvement or resolution
Recoverin, anti-retinal bipolar cells, and other retinal proteins	Photoreceptors, bipolar neurons (recoverin), ganglionic cells	Retinopathy (CAR, MAR)	Small-cell lung cancer, gynecologic cancer (CAR), and melanoma (MAR) [82, 83]	Few cases reported to have moderate response with stabilization
Synaptic antibodies				
Amphiphysin	Presynaptic nerve terminal, central, and peripheral neurons	Stiff person syndrome Encephalomyelitis	90% [28] Small-cell lung cancer, melanoma, breast cancer	Moderate, 60% of the patients show some neurological improvement

has been suggested that prompt diagnosis and treatment while inflammatory process is still active and neurological symptoms are still progressing might be beneficial and even result in clinical improvement [13, 30, 31].

Onconeuronal Antibodies and Associated PNS

Antibodies, Nomenclature, and Target Antigens

The nomenclature of onconeuronal antibodies varies among different groups or authors. Traditionally, these antibodies have been named after the last name of the patient from whom the antibody was firstly identified (e.g., Hu, Yo, Ri, etc.). Some of these antibodies are also known by the name of the protein they target, for example, CV2 antibodies are also called collapsin response mediator protein (CRMP) 5. Some authors [32] proposed a generic nomenclature based on the target cell type (neuronal, glial) and location of the intracellular target antigen (nuclear, cytoplasmic), followed by the chronological order of discovery, for example, Hu antibody has been the first nuclear antibody described, and it is thus referred to as ANNA-1 (antinuclear neuronal antibody-1). Similarly, Yo antibodies are also referred to as PCA-1 (Purkinje cell cytoplasmic antibody type 1). Table 16.2 shows both the traditional and generic nomenclatures for each of these antibodies.

Onconeuronal antibodies are mainly of IgG class [33], although some patients can harbor antibodies of IgM and IgA classes. These antibodies react with a variety of intracellular antigens, located in the nucleus or cytoplasm of neurons, although some of these antigens (such

as Tr or delta/notch-like epidermal growth factor-related receptor [DNER]) carry transmembrane or extracellular portions. Although the identity of these antigens (and the related gene) is known for most onconeuronal antibodies, the exact function of these proteins in neurons and in tumor cells is still unclear [34]. It is important to underline that these antibodies differ from neuronal cell surface antibodies discussed in Chap. 12, which target antigens located in the outer part of the neuronal cell membrane, such as synaptic neurotransmitter receptors (e.g., N-methyl-D-aspartate receptor or NMDAR). Indeed, these neuronal cell surface antibodies have also been identified in patients with neurological syndromes, but their association with cancer is less constant than for onconeuronal antibodies.

Most onconeuronal antibodies are detected in both serum and CSF, with higher titers in CSF (intrathecal synthesis) [35], and in patients with CNS involvement compared to those with peripheral neuronopathy [36]. Overall, antibody titers do not seem to correlate with the severity of neurological symptoms at onset or with outcome, and antibodies might persist despite successful treatment of the tumor and neurological improvement [17]. Thus, serial determination of antibody titers is not recommended [37].

Some of these antibodies are considered markers of the presence of a tumor, such as Hu antibodies, which can be identified in the serum of patients with small-cell lung cancer (SCLC), with or without PNS, although titers are much higher in patients with PNS [38]. On the other hand, other antibodies, such as Yo, are markers of the paraneoplastic neurological syndrome, as they are found in patients with gynecologic tumors only if associated with PNS.

In the following section, we will discuss onconeuronal antibodies associated with PNS involving the CNS, divided according to the localization of their targets (nuclear, cytoplasmic, or synaptic), then we will summarize those associated with PNS involving the visual system, and finally we will briefly describe those antibodies that are only rarely associated with cancer.

Antinuclear Neuronal Antibodies

Hu (ANNA-1) Antibodies

Patients with PNS associated with Hu antibodies can manifest symptoms involving any part of the central and peripheral nervous system. The most frequent anti-Hu PNS is sensory neuronopathy (see *Clinical Case 2*). It occurs in half of the patients and typically starts distally in the limbs, asymmetrically, and progressively extends to the trunk (and face). It generally involves all sensory modalities, affecting simultaneously both small and large nerve fibers. However, in some cases, one type of fiber can be predominantly involved, which results, for instance, in small fiber painful neuropathy or ataxic sensory ganglionopathy. Motor involvement is frequent but does not usually occur in isolation or as a prominent symptom. Other frequent clinical presentations are cerebellar degeneration, limbic encephalitis (confusion, memory loss, behavioral/personality changes, and MRI bilateral mesiotemporal lobe hyperintensities), encephalomyelitis (combining symptoms of brain and spinal cord involvement), brainstem encephalitis, and autonomic dysfunction, each of these syndromes occurring in 10–20% of the patients [5, 39, 40]. Less typical neurological findings include, among others, cranial nerve palsy, ophthalmoplegia, and orolingual tremor. Overall, neurological symptoms develop subacutely, with a median of 8 weeks from onset to peak of disease [40].

Cancer is found in more than 90% of the patients, and it is often diagnosed 4–6 months after onset of neurological symptoms [5, 40]. SCLC is the most frequently identified tumor, whereas extrathoracic tumors are much less common [40].

Response of PNS to tumor treatment is generally poor and at best prevents further impairment of neurological symptoms. Complete remission of the tumor has been identified as the only predictor of PNS stabilization, whereas adding immunotherapy does not appear to affect survival nor neurological outcome [41]. Patients older than 60 years, with a multifocal or more severe

neurological involvement (Rankin scale >3) and who have not received tumor treatment, are at higher risk of mortality [5]. In a study analyzing autopsies from patients with anti-Hu PNS, the cause of death did not appear to be related to the SCLC, given that the tumor was small and most often limited to the chest at onset and during the disease course, but was rather related to brainstem dysfunction (central hypoventilation, aspiration pneumonia due to dysphagia) or severe dysautonomia [40]. This critical neurologic involvement might explain why patients with anti-Hu PNS and SCLC, who seem to have an efficient immune control of the tumor, have a mortality rate similar to patients with SCLC without PNS, who most die from tumor progression [40, 41].

Hu antibodies target a family of proteins that are highly expressed in the central and peripheral nervous system and that are also expressed by SCLC and other tumor cells (Fig. 16.2) [42]. The function of these proteins has only been partly elucidated, but it seems to be related to alternate splicing and regulation of mRNA stability [43, 44]. In neurons, Hu proteins are involved in cellular differentiation and plasticity and are thought to play a role in learning and memory processes [45–47].

Ri (ANNA-2) Antibodies

The typical PNS associated with Ri antibodies, which are much less common than Hu antibodies, is opsoclonus-myoclonus syndrome (OMS). OMS is a rare syndrome characterized by multidirectional, conjugate, erratic, rapid movements of the eyes (opsoclonus), associated with myoclonic jerks and trunk ataxia. A study on 28 patients with anti-Ri PNS described additional symptoms, including brainstem dysfunction, apart from OMS, such as dysphagia, laryngospasm, ophthalmoplegia, and cranial nerves palsies; myelopathy; movement disorders (cervical and jaw-opening dystonia); or seizures [22]. Patients manifesting with stiff person syndrome have also been reported [48].

OMS has been typically associated with neuroblastoma in children, whose serum is most often negative or in some cases harbor Hu or Yo antibodies. By contrast, Ri antibodies are found almost exclusively in adults and are associated with other tumors such as breast cancer, lung cancer, and others. Ri antibodies frequently cooccur with other onconeuronal antibodies (such as Hu, ANNA-3, CV2/CRMP-5, and P/Q voltage-gated calcium channel [VGCC]) [22]. Unlike anti-Hu PNS, tumor treatment, with or without immunotherapy, often results in neurological improvement and decrease of antibodies [22, 49]. In few cases in whom no tumor is found, OMS may remit spontaneously. This different response to therapies of anti-Hu compared to anti-Ri PNS might be related to irreversible (versus reversible) effects on neurons. Indeed, in vitro studies have shown that, although both Hu and Ri antibodies are internalized by live slice-cultured neurons, only Hu antibodies are associated with neuronal death, whereas Ri antibodies seem to cause reversible neuronal dysfunction without affecting cell survival [50].

Ri antibodies react with the nuclei of neurons within the central, but not peripheral, nervous system [51]. Their target proteins (Nova-1 and Nova-2) are highly expressed in the brainstem, spinal cord, and cortex and also by several tumors (SCLC, breast, ovarian, and lymphoma) [52–55]. These proteins modulate inhibitory synaptic receptors (such as gamma-aminobutyric acid $[GABA]_A$ or glycine receptors) and seem involved in long-term potentiation and motor responses [56].

Ma2 (and Ma1) Antibodies

PNS associated with Ma2 antibodies typically occur in young previously healthy men who develop limbic encephalitis, diencephalic encephalitis with hypothalamic dysfunction (excessive daytime sleepiness, narcolepsy-cataplexy episodes), basal ganglia (chorea, parkinsonism), or brainstem encephalitis, either isolated or in combination. Brainstem dysfunction includes prominent eye movement abnormalities (occurring in more than 90% of the patients) ranging from focal oculomotor palsies or vertical gaze palsy to complete external ophthalmoplegia. Brain MRI is abnormal in more than 70% of patients, showing T2/FLAIR (fluid-

attenuated inversion recovery) hyperintensities in the hippocampus, hypothalamus, or brainstem [3].

Tumor is found in 90% of patients, half of them having a testicular germ cell tumor. If no testicular tumor (or other Ma2-expressing cancer) is found, elective orchiectomy should be considered in patients younger than 50 years, with clinical and MRI findings suggestive of Ma2 encephalitis, confirmed Ma2 antibodies, and who show progressive neurological symptoms, new testicular enlargement, or risk factors for testicular tumor, such as cryptorchidism or testicular microcalcifications [11].

Ma2 antibodies target proteins that are highly expressed in the CNS and in testicular germ cells. These antibodies are usually found in both serum and CSF of patients, especially those manifesting with limbic encephalitis. Some patients may harbor additional Ma1 antibodies and are more likely to develop cerebellar symptoms and to have an underlying tumor other than testicular, including lymphoma [3].

Tumor treatment may lead to neurological improvement in a proportion of patients. In a study of 38 patients with anti-Ma2 encephalitis, cancer treatment or immunotherapy resulted in symptom improvement or stabilization in 60% of them (few patients showing a complete recovery) [3]. This study found that age younger than 45, male gender, complete (testicular) tumor response, and absence of additional Ma1 antibodies were factors associated with favorable outcome.

Other Neuronal (and Glial) Nuclear Antibodies

Antibodies targeting zinc-finger protein 4 (ZIC4) are found in patients with SCLC and PNS [57]. In most patients these antibodies coexist with Hu or CV2/CRMP5 antibodies and are associated with encephalomyelitis. However, when they occur in isolation, ZIC4 antibodies are associated with prominent cerebellar dysfunction [23].

SOX1 antibodies are onconeuronal antibodies that are highly predictive for PNS associated with SCLC. They are also known as AGNA-1 (anti-glial/neuronal nuclear antibody type 1) because they not only react with nuclei of neurons but also with glial cells. SOX1 antibodies most frequently identify patients with SCLC and LEMS but can also associate with other neurological syndromes including limbic encephalitis, cerebellar ataxia, sensory neuronopathy, and OMS. Also SOX2 antibodies have been identified in patients with similar neurological syndromes and SCLC [58]. Importantly, SOX1 (or SOX2) antibodies are not found in patients with LEMS or other PNS without cancer [59]. Thus, SOX1 seropositivity can be helpful in identifying patients at risk for SCLC, and, if no cancer is apparent at initial workup, it should prompt search for occult SCLC.

Neuronal Anticytoplasmic Antibodies

Yo (PCA-1) Antibodies

Yo antibodies are one of the most common and characteristic onconeuronal antibodies. The typical anti-Yo PNS is a rapidly progressive pancerebellar syndrome occurring in middle-aged previously healthy women (see *Clinical Case 1*). Cerebellar symptoms usually start as mild difficulties in walking on irregular floors or in high heels and evolve over days or weeks to inability to walk or stand unassisted, with many patients becoming severely disabled (mRS > 3) within the first 3 months of the disease [24]. Some patients may show additional neurological symptoms including dysphagia, bilateral facial palsy, and movement or motor disorders. Brain MRI is usually normal at diagnosis but shows cerebellar atrophy as disease progresses (Fig. 16.2), correlating with dramatic loss of Purkinje cells observed in autopsies.

Anti-Yo PNS usually precede the diagnosis of breast or gynecologic tumor, which is found in more than 90% of female cases. Occurrence of anti-Yo PNS is exceptional in men, in whom it has been associated with gastrointestinal tumors [60]. Unlike Hu antibodies, which are found in a significant proportion of patients with SCLC and no PNS, Yo antibodies are only rarely found (<2%) in patients with gynecologic tumors without neurological syndrome [61]. Yo antibodies

usually occur in isolation and do not coexist with other onconeuronal antibodies [62].

Yo antibodies target cerebellar degeneration-related antigen 2 (CDR2) and its paralog CDR2L, which is involved in c-Myc-dependent regulation of cell cycle. These antibodies intensively react with the cytoplasm of Purkinje cells, visualized as a granular staining, and also with neurons of the deep cerebellar nuclei.

Treatment of the underlying tumor may result in stabilization of the neurological syndrome. Adding immunotherapy has been shown to decrease the levels of Yo antibodies in serum, but not CSF [35], and to improve neurological symptoms in some cases [62–64], especially if started early after disease onset, when patients are not yet severely disabled [29]. However, a series of 34 patients with long-term follow-up failed to demonstrate any beneficial effect of immunotherapy on survival or neurological outcome [24]. In this study, patients younger than 60 years and who had breast cancer had longer survival compared to older women with gynecologic cancer (8 years versus less than 2 years). The cause of death was related to disabling PNS in a quarter of the patients and to tumor progression in half of them.

Tr (DNER) Antibodies

Tr antibodies, also known as DNER, have been associated with paraneoplastic cerebellar degeneration and Hodgkin's lymphoma and are not found in patients with PNS without Hodgkin's lymphoma or with Hodgkin's lymphoma without PNS [26]. These antibodies react with Purkinje cells of rat, but, unlike Yo antibodies, they show a characteristic punctate/dotted staining, which also involve the molecular layer of the cerebellum, but not the deep cerebellar nuclei. They are generally found in both serum and CSF, although few patients have been reported to harbor only CSF antibodies [65]. The target antigen of these antibodies is unknown.

Tumor treatment results in antibody titer decrease and stabilization of cerebellar symptoms, which most often remain disabling [66, 67]. Immunotherapy, and in particular plasmapheresis, may lead to neurological improvement in patients who did not respond to chemotherapy and corticosteroids or immunoglobulins [68].

PCA-2 (MAP1B) Antibodies

Most patients with PCA-2 antibodies develop limbic encephalitis, cerebellar degeneration, sensorimotor neuronopathy, dysautonomia, or LEMS, generally associated with SCLC. PCA-2 antibodies react with Purkinje neurons, dentate cerebellar nucleus, and enteric neurons with a reticular pattern, which, unlike Yo antibodies, extends to dendrites. PCA-2 antibodies often co-occur with other neuronal antibodies, including P/Q-type voltage-gated calcium channels (VGCC), Hu, CV2/CRMP5, and others [25, 69]. PCA-2 antibodies have been recently recognized to target microtubule-associated protein-1-B (MAP1B) [25], which is thought to be involved in neuronal development and differentiation, including dendritic spine formation and synaptic maturation. Treatment of SCLC with or without immunotherapy has been reported to stabilize or, in some cases, improve the neurological symptoms [25].

CV2 (CRMP5) Antibodies

CV2 antibodies, also known as CRMP5, have been associated with several neurological paraneoplastic manifestations involving the central and peripheral nervous system. These include limbic encephalitis, cerebellar degeneration, myelitis, peripheral neuropathy, dysautonomia, and chorea [70]. However, the most characteristic finding is ocular involvement, most frequently optic neuropathy, but also retinitis, uveitis, or vitreitis. These PNS occur in both women and men, and the most frequent associated tumors are SCLC and malignant thymoma, although other tumors have also been reported. In patients showing CNS involvement, CV2/CRMP5 antibodies are found in higher titer in CSF compared to serum [71]. At low titers they can be identified in the serum of patients with tumor but no PNS (5% of patients with SCLC and 12% of those with thymoma), although their presence does not seem to affect tumor outcome [72].

These antibodies react with glial cells and neurons of the neocortex, cerebellum, and optic

nerve, and they target one of the CRMP proteins.

Anti-CV2/CRMP5 PNS can respond to tumor treatment and immunosuppression and in some cases result in complete resolution of the neurological syndrome [73].

Antibodies to Protein Kinases

PNS associated with antibodies to protein kinases have also been described, including anti-protein kinase C gamma (PKCγ[gamma]) in two patients with lung or liver adenocarcinoma and cerebellar degeneration and anti-serine/threonine kinase (BRSK2) in a patient with limbic encephalitis and SCLC [74–76].

Neuronal Antibodies to Synaptic Targets

Antibodies Targeting Amphiphysin and Other Synaptic Proteins

Amphiphysin is a vesicular protein highly concentrated at the synaptic terminal. Antibodies targeting amphiphysin are typically found in patients with stiff person syndrome (SPS) associated with SCLC or breast cancer [28]. This syndrome is less common than the non-paraneoplastic form associated with GAD65 antibodies (see below). Patients with both paraneoplastic and non-paraneoplastic SPS (described in detail in Chap. 30) develop progressive symmetric muscle rigidity involving axial and proximal limbs, associated with painful spasms. Muscle stiffness is usually symmetric, although cases with prominent asymmetric or distal involvement or partial syndromes (e.g., "stiff limb syndrome") have also been reported. Compared to GAD65 antibody-related SPS, patients harboring amphiphysin antibodies are more likely to be female, to experience early severe pain, to have distal muscle or cervical involvement, and to be refractory to spasmolytic treatment [77].

Amphiphysin antibodies can coexist with other onconeuronal antibodies (CV2/CRMP5 and P/Q VGCC) and have also been reported in patients manifesting with paraneoplastic neuronopathy, myelitis, encephalomyelitis, and cerebellar syndrome [28, 78].

Symptomatic treatment of SPS includes high-dose benzodiazepines or other GABA-enhancing drugs (such as valproate, vigabatrin, gabapentin, levetiracetam, tiagabine) and spasmolytic agents (such as baclofen). Partial syndromes may benefit from local botulin toxin injection. Tumor treatment and immunotherapy often result in improvement and, in some cases, resolution of neurological deficits [28].

Antibodies to other synaptic proteins have been reported in few patients and include: gephyrin, associated with SPS and mediastinal carcinoma; synaptophysin, associated with sensory-motor and autonomic neuronopathy and SCLC; and synaptotagmin, associated with LEMS and SCLC [79–81].

Antibodies Associated with Visual System PNS

PNS may affect all segments of the visual system, especially the retina and optic nerves. The most common PNS affecting the retina is cancer-associated retinopathy (CAR). CAR occurs with a variety of tumors (most frequently SCLC and gynecologic cancers) and is associated with antibodies targeting the photoreceptor protein recoverin and less frequently also several other targets (alpha-enolase, rhodopsin, etc.). Patients with CAR develop painless visual loss over days or weeks, affecting both eyes, usually asymmetrically, and are accompanied by photosensitivity, night blindness, photopsia, loss of color vision, and scotomas, resulting from damage to both rods and cones [82]. Recoverin antibody-associated CAR usually precedes the diagnosis of cancer, which is not the case for CAR associated with other retinal antibodies or for melanoma-associated retinopathy (MAR), which is more likely to occur in patients with known melanoma. Compared to patients with CAR, those with MAR show less severe visual loss and can develop exudative retinal detachment [83]. MAR is associated with antibodies against bipo-

lar cells, which are more likely in patients with advanced stage of melanoma. Tumor treatment and immunotherapies have a little effect on both CAR and MAR.

Antibodies Associated with Neurological Symptoms That Are Rarely Paraneoplastic

Although most neuronal antibodies targeting intracellular antigens are associated with paraneoplastic neurological syndromes, few of them are found in patients with neurological manifestations that are only rarely accompanied by cancer. This is the case of antibodies targeting GAD65 or adenylate kinase 5 (AK5).

GAD65 Antibodies

GAD65 is an enzyme that coverts glutamate into GABA. It is abundantly expressed in neurons of the CNS and in pancreatic islet cells. GAD65 antibodies have been found in patients with autoimmune type I diabetes, as well as patients with autoimmune neurological syndromes [84], including stiff person syndrome, cerebellar ataxia, limbic encephalitis, and autoimmune epilepsy [85]. In patients with autoimmune neurological manifestations, GAD65 antibodies are found in both serum and CSF (with evidence of intrathecal synthesis) and at 100–1000 times higher titers than in patients with autoimmune diabetes, in whom these antibodies are usually found only in serum [86, 87].

Less than 5% of the patients with GAD65 antibody-associated neurological syndromes, and in particular stiff person syndrome, have an underlying cancer.

Unlike the aforementioned onconeuronal antigens, which are intracellular and thus inaccessible to circulating antibodies, synaptic targets such as GAD65 (or amphiphysin) might be accessible to circulating antibodies during synaptic vesicle fusion and endocytosis. This suggests that GAD65 antibodies and amphiphysin antibodies might play a pathogenic role, as supported by experimental evidence of both antibodies affecting neuronal function in vitro and amphiphysin antibodies causing neurological symptoms in animal models [88].

AK5 Antibodies

Antibodies to AK5 were firstly identified in the serum and CSF of two patients without cancer who developed limbic encephalitis not responsive to immunotherapy [89]. A recent study confirmed these findings in ten patients [90], most of whom showed inflammatory CSF with elevated tau protein levels, indicating neuronal death. Immunotherapy was ineffective in all but one patient, and in most cases the disease evolved to severe cognitive dysfunction, associated in some patients with hippocampal atrophy.

Conclusion

PNS manifest with several clinically defined neurological syndromes associated with cancer. Recognition of the associated neuronal antibody is important because it can orientate the search for an underlying tumor and has prognostic implications, some antibodies (e.g., Ri- or CV2/CRMP5-associated PNS) being associated with better outcomes than others (e.g., Hu or Yo antibodies). Although most PNS have a poor response to immunotherapy and cancer treatment, early diagnosis and treatment can allow stabilization of the symptoms and prevent progression of neurological disability.

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