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Abstract

In this chapter, we summarise the current knowledge about a group of clinically diverse neurological syndromes that are unified by a common pathophysiology, mostly immune-mediated neuronal dysfunction or degeneration triggered by a distant tumour and thus are coined paraneoplastic neurological syndromes (PNS). In

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the majority of cases, antibodies against onconeural, intracellular antigens expressed by the tumour and the nervous system can be detected in serum and cerebrospinal fluid. Some clinical pictures are suggestive of an underlying PNS. These syndromes include progressive cerebellar degeneration, encephalomyelitis, limbic encephalitis, opsoclonus-myoclonus syndrome, subacute sensory neuronopathy, chronic gastrointestinal pseudo-obstruction and Lambert-Eaton myasthenic syndrome. These clinical manifestations are called classical paraneoplastic syndromes. Other neurological syndromes like brainstem encephalitides or neuropathies can have diverse aetiologies, amongst which a tumour-triggered immune response is one possibility amongst many others. The detection of onconeural antibodies in suspected PNS confirms the diagnosis and aids in diagnosis, tumour search and therapy. Here, we summarise the practical approach, typical findings and the most important syndromes including electrophysiological tests, imaging and cerebrospinal fluid analysis. Not obligatorily paraneoplastic autoimmune encephalitides associated with antibodies against neuronal surface proteins are covered by a separate chapter of this book.

21.1 Definition and Introduction

By definition, all neurological complications of a neoplastic disorder that are not caused by (1) direct compression or infiltration of neuronal structures by tumour cells, (2) metabolic derangements, (3) toxic treatment effects or (4) infections are called “paraneoplastic”. However, the current use of the term “paraneoplastic neurological syndrome (PNS)” generally implies an immune-mediated aetiology of neurological dysfunction or neurodegeneration that is triggered by an underlying tumour. In 1985, Graus and colleagues discovered that some of these cases harbour a distinct antibody in their serum that labels neuronal nuclei (Graus et al. 1985). This antibody became known as anti-Hu (Graus et al. 1987) or antineuronal nuclear antibody 1 (ANNA1) (Kimmel et al. 1988). Subsequently, additional antibodies associated with this or other paraneoplastic neurological syndromes were discovered, the second of which was the anti-Yo antibody. The anti-Yo antibody recognises the CDR (cerebellar-degeneration-related) 34 and 62 proteins expressed in Purkinje cells (Cunningham et al. 1986). It occurs in patients with mostly gynaecological tumours and subacute cerebellar degeneration (Anderson et al. 1988a). Within the following decades, the number of different antineuronal antibodies associated with PNS grew. Whereas the antibodies characterised first are named by the first two initials of the index patients (Hu = Hull, Ri = Richards, Yo = Young (Luque et al. 1991)) or by the order of detection (antineuronal nuclei antibody (ANNA)-1, ANNA-2 and Purkinje cell antibody (PCA)-1 (Lennon 1994), respectively, later on the names indicate the name of the proteins recognised by the antibody (e.g. anti-CRMP5 (Yu et al. 2001)). As a general rule, the more recently the antibodies were characterised, the rarer they occur. Currently, these “classical paraneoplastic antibodies” are categorised into two different subgroups: (1) well-characterised onconeural antibodies with a high probability of an underlying malignancy and (2)

partially characterised onconeural antibodies with an unknown specificity for a tumour because of small numbers of reported patients. This classification, which was introduced in 2004, does not encompass the novel “synaptic” encephalitis syndromes with antibodies against neuronal surface antigens which occur with and without underlying tumours. For systematic reasons, this latter group of autoimmune encephalitides is discussed in detail in Chap. 6 of this book.

21.2 Practical Approach and General Aspects

Paraneoplastic neurological syndromes are rare diseases. Thus, the a priori chance of a paraneoplastic aetiology is low. Nevertheless, clinical syndromes can be divided into those with a high likelihood of paraneoplastic aetiology and those only rarely associated with underlying cancer. These have been termed “classical syndromes” and “nonclassical syndromes”, which are discussed in detail below (Graus et al. 2004). While classical syndromes, e.g. limbic encephalitis (LE) or progressive cerebellar degeneration (PCD), have a high likelihood of an underlying paraneoplastic aetiology, nonclassical syndromes, e.g. brainstem encephalitis or optic neuritis, are usually caused by other diseases. Red flags for a paraneoplastic aetiology are the presence of a subacute, relentlessly progressive syndrome, consecutive or simultaneous affection of different areas of the central and/or peripheral nervous system and a high individual tumour risk (e.g. smoking, weight loss). Other neurological syndromes have diverse aetiologies, amongst which a tumour-triggered immune response is only one remote possibility. These include brainstem encephalitis, optic neuritis, retinal degeneration, stiff-person syndrome, myelitis and motor neuron disease. Regarding the peripheral nervous system, diverse types of neuropathies including Guillain-Barré syndrome lookalikes and also vasculitic neuropathies, brachial neuritis and autonomic neuropathies can potentially be caused by an underlying malignancy. In some cases, also myasthenia gravis when associated with a thymoma can be regarded as a PNS, as well as some tumour-associated cases of acquired neuromyotonia (Graus et al. 2004).

The first step in the diagnostic workup of a neurological syndrome suspected to be paraneoplastic in origin is to prove its immune-mediated nature and rule out obvious differential diagnoses like meningeal disease, metastasis, toxic or metabolic causes. Next, if clinical suspicion of paraneoplastic aetiology remains high, screening for relevant onconeural or neuronal cell-surface antibodies should be initiated. Their presence or absence helps to further predict the probability and location of underlying cancer. Imaging studies are important to exclude differential diagnoses and in a minority of cases show abnormalities compatible with a PNS. The last step would be a tumour screening guided by the clinical information and antibody status.

Detecting antibodies against onconeural antigens, e.g. Hu, CV2/CRMP5, Yo and amphiphysin, together with a compatible neurological syndrome has a very high specificity for a PNS. However, most syndromes can be associated with different antibodies (Table 21.1) and different syndromes can occur with the same antibody.

Table 21.1 Syndromes of the CNS and relevant well-characterised onconeural or neuronal cell-surface antibodies

	Syndrome	Relevant antibodies
CNS	Subacute cerebellar degeneration 25 %	Hu, Yo, CV2/CRMP5, Ri, Tr ^a , amphiphysin, VGCC
	Encephalomyelitis 6 %	Hu, CV2/CRMP5, amphiphysin
	Limbic encephalitis 10 %	Hu, Ma2, CV2/CRMP5, Ri, amphiphysin
		NMDAR, Lgi1 ^b , CASPR2 ^b , GABA(b)-R, AMPA-R, mGluR5, glyR ^b , GAD ^b
	Opsoclonus-myoclonus syndrome (adults) 2 %	Ri, Hu, Ma/Ta, NMDAR
	Retinopathy 1 %	Hu, CV2/CRMP5, recoverin
Stiff-person syndrome 1 %	Amphiphysin, glyR ^b , GAD ^b	

^aTr antibodies, are not considered well-characterised but should raise a high suspicion of underlying cancer

^bLgi1, GAD' glycine-receptor antibody-associated syndromes are rarely paraneoplastic

In addition, patients with PNS can harbour more than one onconeural antibody in serum and CSF (Pittock et al. 2003). Moreover, specific onconeural antibodies are associated with different types of cancer. The rather complex association of onconeural antibodies, different PNS and underlying cancers is summarised in Table 21.2. Of note, onconeural antibodies like anti-Hu antibodies, although at lower titres than those associated with PNS, occur in patients with tumours but without neurological syndromes (Monstad et al. 2009).

The probability of a PNS depends on (1) the occurrence of a classical or nonclassical syndrome, (2) absence or presence of a detectable tumour and (3) detection of a well-characterised antibody, partially characterised antibody or absence of known antibodies (Fig. 21.1). Classical syndromes and detectable tumours or any syndrome and detectable well-characterised antibodies can be classified as definite PNS. A nonclassical syndrome associated with a malignancy is considered to represent a definite PNS if either a well-characterised or partially characterised antibody can be detected or the neurological sign and symptoms respond to treatment of the underlying malignancy. Other situations can be classified as possible PNS after exclusion of differential diagnoses.

In most patients with PNS, neurological symptoms precede tumour diagnosis, because tumours are too small to be detectable with available techniques. If any classical or nonclassical syndrome co-occurs with a well-characterised onconeural (e.g. Hu, Yo) antibody, initial tumour screening should be carried out according to recently published European guidelines and close oncological follow-up every 3–6 months for 4 years is warranted (Titulaer et al. 2011a). A similar tumour screening approach is advisable for classical syndromes without well-characterised or with partially characterised antibodies. If the syndrome is nonclassical and no antibodies are found, the method of tumour screening and surveillance depends on the level of clinical suspicion and no clear guidelines exist. It is good clinical practice to perform close clinical follow-up visits and possibly repeat tumour screening but alternative diagnoses have to be considered frequently.

Table 21.2 Onconeural antibodies found in paraneoplastic syndromes

Antibody	Antigen	Associated syndromes and symptoms	Most common tumours
<i>Onconeural antibodies (well-characterised, paraneoplastic antibodies tumour in >90 %)</i>			
Anti-Hu (ANNA-1)	HuD	Encephalomyelitis, limbic encephalitis, cerebellar degeneration, brainstem encephalitis, multi-segmental myelitis, sensory neuronopathy, sensory-motor neuropathy, autonomic neuropathy	Lung cancer (85 %), mostly SCLC, neuroblastoma, prostate carcinoma
Anti-Yo (PCA-1)	CDR2, CDR62	Paraneoplastic cerebellar degeneration	Ovarian, breast cancer
Anti-CV2/CRMP5	CRMP5	Encephalomyelitis, polyneuropathy, optic neuritis, limbic encephalitis, choreatic syndromes, cerebellar degeneration	SCLC, thymoma
Anti-Ta/Ma2 ^a	MA-proteins	Limbic encephalitis, rhombencephalitis, m>>f	Testicular cancer
Anti-Ri (ANNA-2)	NOVA-1	Opsoclonus-myoclonus syndrome, rhombencephalitis, cerebellar degeneration, myelitis, jaw dystonia, laryngospasm	Breast, ovarian carcinoma, SCLC
Anti-amphiphysin	AMPHIPHYSIN	Stiff-person syndrome, limbic encephalitis, rhombencephalitis, cerebellar degeneration, polyneuropathy	Breast cancer, SCLC
Anti-recoverin	RECOVERIN	Retinopathy	SCLC
Anti-SOX-1 (AGNA)	SOX-1	Non syndrome-specific	Sensitivity 67 %, specificity 95 % for SCLC in LEMS
<i>Partially characterised onconeural antibodies (antigen not characterised or positive predictive value for tumour unknown)</i>			
Anti-Tr (PCA-Tr)	DNER	Cerebellar degeneration	Hodgkin lymphoma, non-Hodgkin lymphoma
Anti-Zic4	ZIC1-4	Cerebellar degeneration	SCLC
PCA-2	280 kD	Encephalitis, Lambert-Eaton myasthenic syndrome, polyneuropathy	SCLC
ANNA-3	170 kD	Neuropathy, cerebellar degeneration, limbic encephalitis	SCLC

Alternative names are given in brackets

DNER delta/notch-like epidermal growth factor-related receptor

^aIn some patients coexisting Ma1 antibodies, in which case often brainstem syndromes and non-testicular tumours predominate

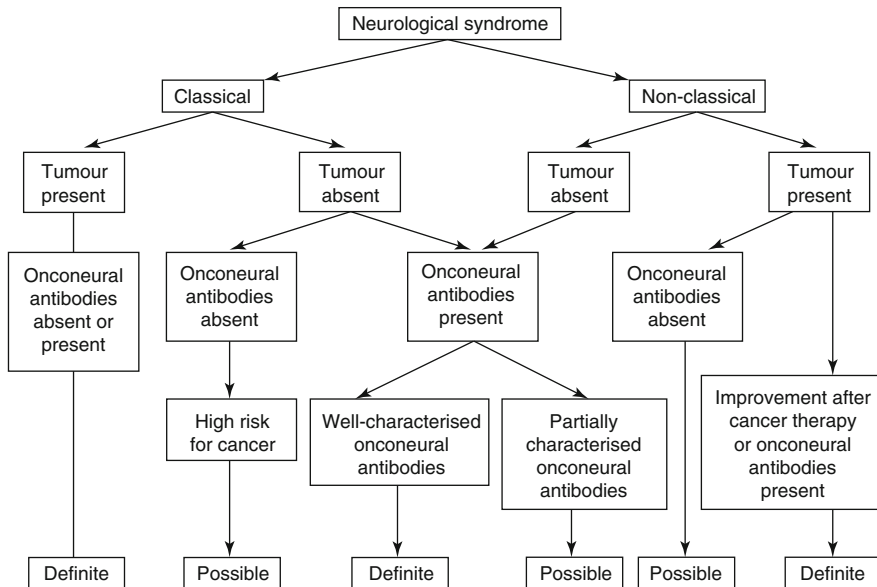


Fig. 21.1 Flow chart showing the level of diagnostic evidence of a paraneoplastic neurological syndrome depending on the neurological syndrome, the presence or absence of onconeural antibodies and a tumour. Of note, a definite and possible PNS without detection of a tumour requires regular tumour screenings for 4 years (Reprinted with permission from Graus et al. (2004))

21.3 Pathophysiology

In most paraneoplastic neurological syndromes described in this chapter, ectopic expression of neuronal antigens by systemic tumours drives an immune-mediated inflammatory response against central or peripheral nervous tissue. These *onconeural* antigens can be expressed by many tumours and most often by tumours of neuroectodermal lineage, e.g. small-cell lung cancer (SCLC). Antitumour immune responses are a common phenomenon, e.g. low titre anti-Hu antibodies are detectable in approximately 16 % of patients with SCLC without neurological symptoms (Dalmau et al. 1990; Graus et al. 1997). However, only a minority of these develop a paraneoplastic neurological syndrome. This might be due to intrinsic tumour factors (degree of inflammation, downregulation of HLA) (Maverakis et al. 2012), which causes breach of tolerance to self antigens. Furthermore, host factors like human leucocyte antigens (HLA) haplotypes likely contribute (Dalmau et al. 1995), but the main factors remain unclear.

Recent years have shown that the subcellular localisation of the detected antigen plays a major role for disease mechanisms. As already mentioned, onconeural antibodies are directed against intracellular antigens. These are not directly accessible to the antibodies. Most likely, the main pathogenic effect is carried out by cytotoxic T cells, resulting in neuronal cell death (Lancaster and Dalmau 2012). There are some exceptions to this rule. Amphiphysin antibodies might have a direct

pathophysiological effect as suggested by *in vivo* models although the antigen is localised intracellularly (Sommer et al. 2005). Conversely, antibodies directed against neuronal surface proteins, δ /notch-like epidermal growth factor-related receptor (DNER), also known as anti-Tr (Greene et al. 2014; de Graaff et al. 2012), and antibodies against metabotropic glutamate receptor 5 (mGluR5) (Lancaster et al. 2011; Graus et al. 2014) can be found in PCD and LE in association with Hodgkin lymphomas (HL), respectively. However, beyond their atypical cellular localisation, the pathophysiology of anti-Tr and anti-mGluR5 antibody-associated PNS might differ with respect to cause of the autoimmune response as, in contrast to other onconeural antibodies, these antigens are not expressed in the underlying tumours (Graus et al. 2014). Nevertheless, this distinction helps to differentiate the paraneoplastic syndromes described in this chapter from the therapy-responsive encephalitis syndromes associated with neuronal surface and synaptic antibodies described in Chap. 6.

In Lambert-Eaton myasthenic syndrome (LEMS), antibodies directed against presynaptic P/Q-type voltage-gated calcium channels (VGCC) directly interfere with proper depolarisation-dependent acetylcholine release within the neuromuscular junction (Titulaer et al. 2011b). In paraneoplastic LEMS, the underlying SCLCs express VGCC (Roberts et al. 1985). However, as antibodies against VGCC also occur in non-paraneoplastic LEMS, which present about 50 % of the cases (Titulaer et al. 2011b), VGCC antibodies are not regarded as onconeural antibodies.

Not all paraneoplastic syndromes involving the nervous system are induced by an immune attack against structures of the nervous system. A notable exception is the POEMS syndrome. This acronym stands for polyneuropathy, organomegaly, edema, M-gradient and skin changes (Li and Zhou 2013). This subtype of monoclonal gammopathy-associated neuropathy normally shows an M-gradient representing IgA lambda. The assumed pathophysiology is a massively increased vascular endothelial growth factor (VEGF) contents in the patient's platelets somehow induced by the neoplastic plasma cells. VEGF is thought to induce a breakdown of the blood-nerve barrier with subsequent influx of serum proteins and demyelination. Highly increased serum VEGF levels are diagnostic.

21.4 Classical and Nonclassical Paraneoplastic Neurological Syndromes

21.4.1 Progressive Cerebellar Degeneration

PCD is one of the paraneoplastic syndromes with onconeural antibodies most frequently encountered in clinical practice (Giometto et al. 2010). Typical PCD clinically presents as a pancerebellar syndrome with both truncal and appendicular ataxia. Although initially, there can be asymmetrical involvement of the limbs, during the course of the disease the ataxia becomes symmetrical. Disability is usually severe so that most patients become unable to walk or even sit without support. Most patients have dysarthria, in part to an extent that speech becomes

unintelligible, and nystagmus (Anderson et al. 1988a). Neurological symptoms progress over a few weeks or months and eventually stabilise, unfortunately most often with severe residual and permanent symptoms due to cerebellar dysfunction (Anderson et al. 1988a). Most patients have other signs of neuronal involvement beyond the cerebellum including extensor plantar responses, hyporeflexia or mild cognitive dysfunction. In some cases, progressive involvement of neuronal structures other than the cerebellum is observed leading to the diagnosis of progressive encephalomyelitis.

In an initial series, approximately 50 % of patients with PCD had detectable antineuronal antibodies upon screening using immunohistochemistry (Anderson et al. 1988a). In a later series of patients positive for antineuronal antibodies, five different antibody specificities were identified in PCD (Shams'ili et al. 2003): anti-Yo antibodies were most frequent, closely followed by anti-Hu antibodies. Anti-Tr (recently identified as directed against DNER) and anti-Ri occurred less often and anti-mGluR1 antibodies were rare. Another well-defined onconeural antibody detected in some cases of PCD is anti-CV2/CRMP5 (Honnorat et al. 1996). In addition, serum and CSF of patients with PCD and SCLC often harbours antibodies against VGCC (Graus et al. 2002) and in some cases against Zic4 (Bataller et al. 2004). Patients with PCD and VGCC antibodies should be examined for the presence of Lambert-Eaton myasthenic syndrome (Mason et al. 1997). One of four cases of anti-Ca/anti-ARHGAP26 antibodies and PCD has been reported to be paraneoplastic because of the coincidence with ovarian cancer (Jarius et al. 2013). In addition, two patients with antibodies against protein kinase C γ , which is highly expressed in Purkinje cells, and cancer have been reported (Sabater et al. 2006; Hoftberger et al. 2013).

The severity of clinical impairment due to cerebellar dysfunction correlates with the antibodies detected. Compared to patients with anti-Yo, anti-Hu and anti-Tr, patients with anti-Ri antibodies retain their ability to walk far more often (Shams'ili et al. 2003). Anti-Ri antibodies were also associated with a lower incidence of dysarthria and nystagmus while anti-Hu positivity was associated with an increased incidence of additional neurological signs and symptoms. The median survival of patients with anti-Yo and anti-Hu antibodies and PCD was 13 and 7 months, respectively. This was much shorter than the survival in the group of patients with anti-Tr antibodies (>113 months). Also patients with anti-Ri-associated PCD tended to live longer. Interestingly, in a subset of patients with anti-Ri and anti-Tr antibodies, symptoms can improve considerably upon treatment (Shams'ili et al. 2003; Bernal et al. 2003), which only rarely occurs in anti-Yo-positive patients (Shams'ili et al. 2003).

Upon histopathological examination, PCD is characterised by a severe and diffuse loss of Purkinje cells throughout the cerebellum associated with CD8+ T-cell infiltrates and microglial activation throughout the brain (Giometto et al. 1997; Storstein et al. 2006).

Usually the neurological syndrome stabilises after several months but functionally on a very poor level with 90 % of patients being wheelchair bound (McKeon et al. 2011a). On magnetic resonance imaging (MRI) early during the disease,

usually no abnormalities are found. Within months, atrophy may develop (McKeon et al. 2011a). In a few cases, fluor-deoxyglucose-positron-emission-tomography (FDG-PET) showed cerebellar hypermetabolism early during the disease (Choi et al. 2006).

The differential diagnosis of PCD is broad. Cerebellar ataxia can evolve as a predominant symptom in many neurological diseases, e.g. spinocerebellar ataxias, multiple system atrophy and non-paraneoplastic immune-mediated cerebellitis associated with antibodies against glutamic acid decarboxylase (GAD). However, paraneoplastic cerebellar degeneration is distinguished from these disorders by its relentless, subacute progression. In addition to its slower progression and indolent course, anti-GAD-positive cerebellar degeneration is also often associated with other autoimmune diseases including diabetes mellitus, thyroiditis and sometimes vitiligo (Honnorat et al. 2001). In some cases, Creutzfeldt-Jakob disease (CJD) can mimic PCD (Grau-Rivera et al. 2014). Cerebellitis of infectious origin, e.g. varicella zoster virus, can initially mimic PCD; however, it usually occurs in children (Bozzola et al. 2014). In rare occasions, HIV infection can induce progressive cerebellar ataxia (Tagliati et al. 1998) or it is caused by infratentorial progressive multifocal leucoencephalopathy in the context of AIDS (Ali et al. 2013) or immunosuppression (Jones et al. 1982). The initial phase of Wernicke-Korsakoff syndrome due to thiamine deficiency can be dominated by subacute ataxia (Butterworth 1993).

21.4.2 Subacute Sensory Neuronopathy

Subacute sensory neuronopathy (SSN) is by far the most frequently encountered PNS affecting the peripheral nervous system (Giometto et al. 2010). This unique syndrome was initially described by Denny-Brown in two cases with neuropathy associated in bronchial carcinoma in 1948 (Denny-Brown 1948). Patients with SSN are characterised by subacutely spreading, frequently asymmetrical, non-length-dependent numbness and paraesthesias, including the face and trunk, which are associated with severe sensory ataxia. About half of the patients report neuropathic pains. Clinically, there is no motor involvement. Due to sensory ataxia, most patients become unable to walk without aid. In addition, frequently dysautonomia is observed. Just recently diagnostic criteria were published, which rely upon the characteristic clinical picture as well as on the typical result obtained in nerve conduction studies (Camdessanche et al. 2009). These reflect the pathophysiology with loss or reduced amplitude of sensory compound nerve action potentials. However, clinically inapparent involvement of motor axons with decreased amplitudes and nerve conduction velocity especially in the lower limb can be observed (Camdessanche et al. 2009). Sensory-evoked potentials are lost in most cases and abnormal when detectable (Camdessanche et al. 2009). Interestingly, upon electrophysiological examination, the masseter reflex in patients with SSN and facial hypaesthesia is unaffected while the blink reflex is abnormal (Valls-Sole et al. 1990). This observation was explained by the fact that perikaryons carrying the input from the masseter spindles are not localised in the trigeminal ganglion, which is affected

by the disease. In contrast, they reside within mesencephalic nucleus of the trigeminal nerve. Thus, they are part of the central nervous system (Ongerboer de Visser 1983).

Approximately 80 % of patients with paraneoplastic SSN harbour anti-Hu antibodies. Other onconeural antibodies usually do not associate with SSN (Molinuevo et al. 1998). Small-cell carcinomas of the lung (SCLC) are by far the most common tumour found in anti-Hu-positive SSN. These are also frequently found in paraneoplastic SSN without known antibodies. In addition, a wide variety of cancers may be associated with SSN, including prostate, breast, pancreatic, neuroendocrine, bladder and ovarian cancer (Rudnicki and Dalmau 2005).

At autopsy, histological examination in SSN shows inflammatory infiltrates including CD8+ T cells in the spinal and autonomic ganglia (Panegyres et al. 1993; Wanschitz et al. 1997).

SSN is distinguished clinically from other forms of predominantly sensory neuropathy by the non-length-dependent development of sensory symptoms. Thus, sensory disturbances frequently involve the upper limb and may also include the face. In addition, sensory involvement is more often asymmetrical and presents predominantly as sensory ataxia. Finally, it is characterised by pronounced axonal loss upon sensory nerve conduction studies in the upper limbs while only minor changes can be found in motor nerve conduction studies (Camdessanche et al. 2009). Non-paraneoplastic SSN can evolve in the context of systemic autoimmune diseases, most often Sjögren's syndrome (Valls-Sole et al. 1990; Griffin et al. 1990). In addition, toxic SSN can occur upon chemotherapy including cisplatin (Gill and Windebank 1998) administered to cancer patients (Krarup-Hansen et al. 2007).

21.4.3 Limbic Encephalitis

The association of LE and cancer was initially described in 1968 by Corsellis et al. (1968). Diagnostic criteria, although not formally validated, include the following criteria: (a) a clinical picture with short-term memory loss, psychiatric symptoms or epileptic seizures suggesting the involvement of limbic structures; (b) an interval <4 years between onset of symptom and the diagnosis of cancer; (c) exclusion of other cancer-related explanations including metastasis, infections, nutritional or metabolic disturbances, cerebrovascular disease or side effect of cancer therapy; and (d) finally, either inflammatory cerebrospinal fluid (CSF) changes, unilateral or bilateral temporal hyperintensities in T2-/FLAIR-weighted MRI or temporal atrophy on T1-weighted images or EEG showing slow or sharp-wave activity in one or both temporal lobes need to underscore either the inflammatory origin or involvement of limbic structures (Gultekin et al. 2000).

In a recent European series, LE occurred in approximately 10 % of all PNS (Giometto et al. 2010). The neurological symptoms evolved in half of the patient before the diagnosis of cancer (Gultekin et al. 2000). Most cases present with short-term memory loss (84 %), seizures (50 %), acute confusional states (46 %) and/or and psychiatric symptoms (42 %) with affective symptoms, hallucinations and

personality changes being most common. Symptoms usually evolve within days and weeks rather than months and years. A subset of patients also develops signs of hypothalamic dysfunction including hyperthermia, weight gain, endocrine dysfunction including diabetes insipidus and hypersomnia. In a few patients, cerebellar or brainstem involvement or neuropathy can occur (Gultekin et al. 2000). Especially in patients with anti-Hu antibodies, the syndrome can eventually evolve into an encephalomyelitis (Graus et al. 2001) (see below).

Anti-Hu antibodies most often associate with SCLC and the prognosis is generally unfavourable. In patients with anti-CV2/CRMP5 antibodies, optic neuritis and chorea can be associated features (Honnorat et al. 1996; Cross et al. 2003). Other onconeural antibodies are anti-Ma2 (also known as anti-Ta) and anti-amphiphysin. Most commonly associated tumours are lung cancers, especially SCLC. However, in women, breast and ovarian cancer are common, and in young male patients, one has to consider testicular cancer (anti-Ma2) (Voltz et al. 1999). Rarely, neuroectodermal skin cancer (Merkel-cell carcinoma) has been described (Greenlee et al. 2002). Furthermore, thymomas and lymphomas have to be considered in onconeural and neuronal cell-surface antibody-associated syndromes (Yu et al. 2001; Lancaster et al. 2011; Ingenito et al. 1990; Irani et al. 2012) (mGluR5, Chap. 6). Importantly, limbic encephalitis can be associated with onconeural (e.g. Hu) and neuronal cell-surface antibodies (e.g. against AMPA receptors, GABA_B receptors, Chap. 6) or a combination of antibodies from both groups (e.g. Hu and GABA_B receptors) (Lancaster and Dalmau 2012). Of the cases with paraneoplastic limbic encephalitis previously considered as seronegative, up to 40 % might harbour anti-GABA_B receptor antibodies (Boronat et al. 2011) (Chap. 6). In summary, in LE it is important to comprehensively test CSF and serum for known and unknown onconeural and neuronal surface antibodies. In cases with definite LE with well-characterised antibodies, about 50 % of the patients died during follow-up, and the minority showed improvement in response to therapy (Bataller et al. 2007). Patients with LE and neuronal surface or synaptic autoantibodies have a far better prognosis (Chap. 6).

In 70–80 % of cases with paraneoplastic LE, neuroimaging studies show medial temporal lobe hyperintensity on fluid-attenuated inversion recovery and T2-weighted images (Gultekin et al. 2000; Lawn et al. 2003). Upon neuropathological examination, brains of patients with classical paraneoplastic LE show neuronal loss, inflammatory infiltrates and microglial nodules in limbic structures including the hippocampus and amygdala (Alamowitch et al. 1997; Newman et al. 1990).

In oligosymptomatic cases of LE, schizophrenia or other psychiatric diseases might be considered as differential diagnosis. In addition, encephalopathy due to intoxication or metabolic disturbance might mimic some aspects of LE as does temporal lobe epilepsy or status epilepticus of complex-partial seizure due to other pathophysiologies. Infectious aetiologies, most importantly herpes simplex encephalitis have to be excluded (Granerod et al. 2010). Human herpes virus type 6 (HHV6) can induce LE-like encephalitis, including typical neuroimaging results, in patients after allogeneic haematopoietic stem cell transplantation (Bhanushali et al. 2013). LE with antibodies against neuronal surface or synaptic proteins

(Chap. 6) are more common than the paraneoplastic LE variants described here (Granerod et al. 2010).

21.4.4 Encephalomyelitis

PCD, SSN as well as paraneoplastic LE can show signs and symptoms suggesting involvement of other parts of the nervous system. Thus, there is a spectrum from more localised syndromes (PCD, LE, SSN) to a widespread affection of the entire nervous system coined encephalomyelitis (EM) (Henson et al. 1965). The latter is characterised by a simultaneous or progressive involvement of different subsystems of the nervous system including the peripheral nervous system. This spectrum is best described in anti-Hu-associated syndromes with underlying SCLCs. Here, one quarter of patients show isolated involvement of the nervous system, while in three quarters of patients either two or three different areas of the nervous system are affected (Dalmau et al. 1992). SSN predominates in about 60 % of the cases, but motor neuron dysfunction, limbic involvement, cerebellar degeneration, brainstem encephalitis and autonomic dysfunction can also be dominating clinical features (10–20 %) (Dalmau et al. 1992). The distinction between encephalomyelitis and localised syndromes, e.g. PCD with minor brainstem involvement, remains somewhat arbitrary. According to the recommended diagnostic criteria, the diagnosis of EM should be avoided in cases with a clearly dominant localised syndrome (Graus et al. 2004) (Fig. 21.2). Nevertheless, the simultaneous or consecutive association of subacute dysfunction of different areas of the nervous system is highly suggestive of a paraneoplastic origin, and thus its recognition as (EM) is helpful for clinical practice.

Most patients suffering from (EM) have anti-Hu antibodies (Graus et al. 2001; Dalmau et al. 1992). However, (EM) was also reported in single cases with anti-CRMP5 antibodies (Honnorat et al. 1996). Although sharing parts of the name, the syndrome of progressive encephalomyelitis with rigidity and myoclonus, which is associated with a different subset of antibodies, is clinically more related with stiff-person syndrome and thus is discussed below.

21.4.5 Opsoclonus-Myoclonus Syndrome

The paraneoplastic opsoclonus-myoclonus syndrome (OMS), also named Kinsbourne syndrome after its first description in 1962 (Kinsbourne 1962), has a characteristic age distribution. Each age group has specific associated antibodies, underlying tumours and prognosis. In paediatric cases, the mean onset is 18–20 months with only 13 % of cases being older than 2 years (Boltshauser et al. 1979; Talon and Stoll 1985). Most of these patients suffer from neuroblastomas but onconeural antibodies are extremely rare. Young adults (median 22 years) have either idiopathic or teratoma-associated OMS and novel neuronal surface antibodies can be found in some of them (Armangue et al. 2014). Adult paraneoplastic cases

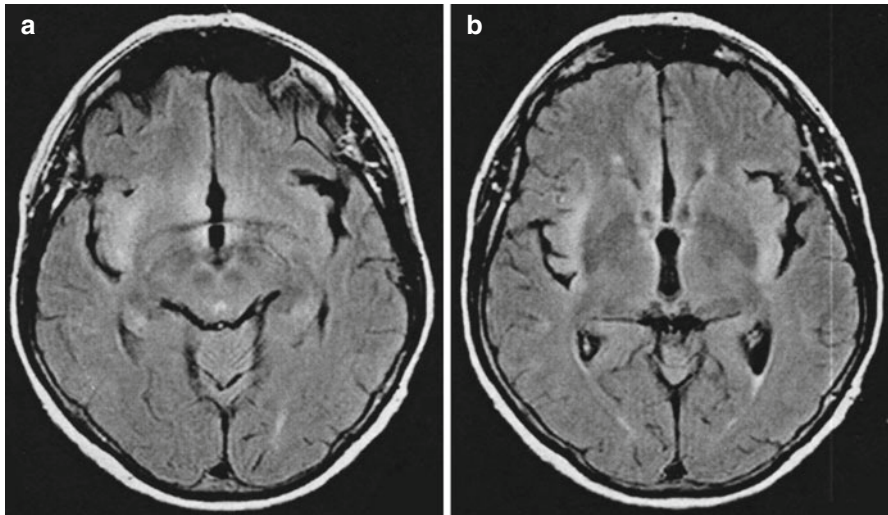


Fig. 21.2 Subclinical involvement of limbic structures in a patient with anti-Hu-associated subacute sensory neuropathy. The 69-year-old female with subacute sensory neuropathy (SSN) and high-titre anti-Hu antibodies presented with the typical clinical picture of SSN with paraesthesias of the limbs and severe sensory ataxia. In addition, mild neuropsychiatric abnormalities including apathy and mental slowness were noted. Cranial MRI (FLAIR) showed hyperintensity of the temporal lobe (a), insular region (a/b) and the gyrus cinguli (b). Although these findings proved that the paraneoplastic syndrome affected areas of the nervous system beyond the spinal ganglia, the diagnosis of SSN not encephalomyelitis was made as the SSN was by far the predominant paraneoplastic syndrome. Although asbestosis was present, no lung tumour could be detected. After short-lived stabilisation in response to high-dose steroids, the patient's conditions deteriorated and she died 5 months after onset of symptoms

associated with other tumours were older than 40 years with a mean age of onset of 66 years reported (Anderson et al. 1988b; Bataller et al. 2001). Generally, paraneoplastic OMS is rare and occurs approximately tenfold less often than PCD or SSN (Giometto et al. 2010).

Opsoclonus is an ocular movement disorder defined by continuous, irregular and conjugated chaotic back-to-back saccades in all direction but preferentially horizontally without intersaccadic interval. Opsoclonus is normally increased by eye closure and fixation and persists during sleep (Bellur 1975). In OMS, opsoclonus is typically associated with action myoclonus of the extremities; also, asterixis may occur (Caviness et al. 1995). The neuronal generators of opsoclonus and myoclonus are distinct as there is no temporal association. In addition, opsoclonus and myoclonus are often associated with ataxia, which in comparison to PCD has been reported to be more truncal than appendicular (Anderson et al. 1988b). However, in many cases the presence of ataxia is difficult to ascertain due to severe myoclonus. Thus, its presence has even been questioned with the ataxic movement disorder interpreted rather as a result of the myoclonus (Pranzatelli 1992). The onset of OMS is usually subacute within days or weeks. Initially, patients frequently complain of vertigo. Both oscillopsias due to opsoclonus and stance and gait instability due to

myoclonus (and ataxia) can become so severe that the patients lose their ability to walk unaided and prefer to lie supine with their eyes closed (Pranzatelli 1992). Encephalopathy has been reported repeatedly in OMS with altered mental status in the sense to apathy, lethargy or confusion occurring in approximately half of adult cases and progressing to stupor or coma in a minority of these. Dysphagia and dysarthria may be present (Pranzatelli 1992). Children that survive OMS frequently have neurological, neurocognitive and behavioural deficits, which can be severe in some cases (Hayward et al. 2001). If the tumour is not treated, patients with adult paraneoplastic OMS usually die from encephalopathy; antineoplastic treatment can improve symptoms considerably (Bataller et al. 2001).

Only a minority of both adult and paediatric patients with paraneoplastic OMS harbour antineuronal antibodies (Bataller et al. 2001; Antunes et al. 2000). The most common antibody found to be associated with adults paraneoplastic OMS is anti-Ri, which in a review of published cases occurred in 66 %. Much less often, anti-Hu and anti-amphiphysin as well as VGCC antibodies are found (Klaas et al. 2012). Neuronal surface antibodies of unknown specificity have been observed in young adult patients with teratomas or testis tumours (Armangue et al. 2014). In single cases, OMS might be part of the clinical presentation of NMDA receptor-antibody-associated encephalitis (Kurian et al. 2010; Smith et al. 2011); however, no tumour has been detected in these two cases, a patient with OMS and GABA_B receptor antibodies (DeFelipe-Mimbrera et al. 2014) and OMS with GAD antibodies (Bhandari 2012). In addition, diverse autoantigens, including proteins of the post-synaptic density, have been found in paraneoplastic and non-paraneoplastic OMS but currently do not have diagnostic relevance (Bataller et al. 2003). In paediatric paraneoplastic OMS, cases with onconeural antibodies showed anti-Hu (Antunes et al. 2000; Fisher et al. 1994). In addition, antibodies against neurofilament (Connolly et al. 1997) and the cell surface of granule cells (Blaes et al. 2005) have been reported in paediatric OMS. However, the clinical or pathophysiological relevance of these findings remains to be explored.

Diverse tumours have been found associated with adult paraneoplastic OMS (Pranzatelli 1992). Lung cancer is the most frequent cancer followed by breast cancer (Klaas et al. 2012). Paediatric cases are associated with neuroblastoma, ganglioneuroblastoma or ganglioneuroma (Pranzatelli 1992). About 2 % of children with neuroblastomas develop OMS, and this is associated with a more favourable prognosis of the tumour (Altman and Baehner 1976).

Neuroimaging studies most frequently reveal pontine lesion in adult OMS (Kim et al. 2009; Hattori et al. 1988). Children with paraneoplastic OMS usually develop persisting cerebellar atrophy (Hayward et al. 2001) (Fig. 21.3).

Autopsy findings in paraneoplastic OMS did not reveal any specific abnormalities. Mostly, they report diffuse microglial proliferation and lymphocytic infiltrates in different brain areas including the cerebellum and brainstem (Anderson et al. 1988b; Young et al. 1993). However, mild Purkinje cell loss has been reported in some cases (Anderson et al. 1988b).

In adults, only a minority of cases with OMS are paraneoplastic (Klaas et al. 2012), whereas up to 40 % of children with OMS have neuroblastomas or related

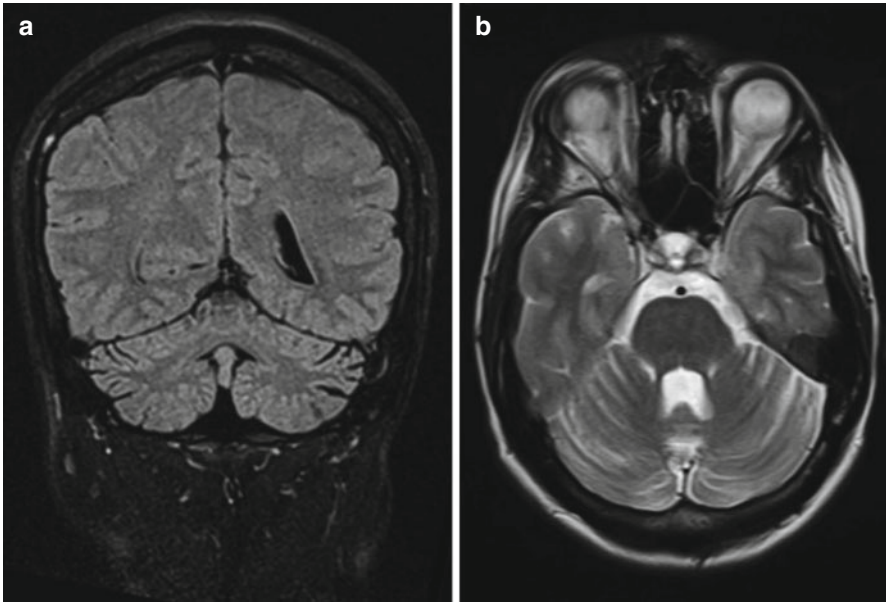


Fig. 21.3 Cerebellar atrophy as a residuum of childhood opsoclonus-myoclonus syndrome associated with neuroblastoma. Cranial MRI: (a) coronar FLAIR and (b) horizontal T2-weighted images. The 30-year-old female developed opsoclonus-myoclonus syndrome (OMS) at the age of 18 months. Several months later, a neuroblastoma of the left adrenal gland was diagnosed and surgically removed. After surgery and steroid therapy, the patient rapidly improved. However, cerebellar ataxia and behavioural-developmental deficits remained. Although the patient became ambulatory, frequent falls persist. The patient is independent regarding activities of daily living; however, no school-leaving graduation could be obtained

tumours (Brunklaus et al. 2012). The rest remains idiopathic or infectious, parainfectious or toxic/metabolic (Pranzatelli 1992; Klaas et al. 2012). Infectious causes include HIV seroconversion, poliomyelitis, EBV, CMV, mumps, HHV6, West Nile virus and others (Pranzatelli 1992; Klaas et al. 2012; Belcastro et al. 2014; BirluTiu and BirluTiu 2014). A number of intoxications, including amitriptyline, lithium and carbamazepine, were found to induce OMS (for a more complete list, compare (Pranzatelli 1992)). The clinical course of non-paraneoplastic OMS is usually monophasic and, if the underlying infection is not life threatening, mostly benign.

21.4.6 Chronic Intestinal Pseudo-obstruction

Chronic intestinal pseudo-obstruction (CIPO) is subsumed under dysautonomia in epidemiological overviews about PNS (Giometto et al. 2010). Dysautonomia is a rather rare feature in PNS occurring approximately fivefold less often than SSN and as often as LEMS (Giometto et al. 2010). Thus, it can be concluded that paraneoplastic CIPO is even rarer. The first study indicating that CIPO can occur in the context of a PNS was reported in 1978 (Ahmed and Carpenter 1975). Soon, this was

followed by larger case series of patients with SCLC or, in rare occasions, pulmonary carcinoids (Chinn and Schuffler 1988).

Per definition, CIPO is a clinical syndrome presenting with symptoms and signs of intestinal obstruction in the absence of mechanical blockade (Schuffler et al. 1981). Frequent complaints of patients with paraneoplastic CIPO are nausea and vomiting, abdominal pain and distension and severe obstipation. In some patients, additional neurological symptoms occur including other signs of dysautonomia including neurogenic bladder and orthostatic hypotension. Also peripheral neuropathy, cognitive disturbances or ataxia have been noted (Chinn and Schuffler 1988).

In a large series of 162 patients with PNS and anti-Hu antibodies, approximately 10 % presented with solely gastrointestinal symptoms (Lucchinetti et al. 1998). Some patients with medium to high titres of antibodies against $\alpha 3$ acetylcholine receptor antibodies develop limited dysautonomia with gastrointestinal dysmotility (McKeon et al. 2009).

The most frequent tumour associated with CIPO is SCLC (Lucchinetti et al. 1998; Lennon et al. 1991). CIPO has also been reported in a younger patients in association with neural crest tumours (Gohil et al. 2001), e.g. a ganglioneuroblastoma associated with high anti-Hu titres (Wildhaber et al. 2002). Dysautonomia with $\alpha 3$ acetylcholine receptor antibodies is frequently non-paraneoplastic but can occur in association with diverse tumours, most often adenocarcinomas (McKeon et al. 2009) but also thymomas (Rakocevic et al. 2003). CIPO in the context of a thymoma is sometimes associated with myasthenia gravis (Rakocevic et al. 2003; Kulling et al. 1997; Musthafa et al. 2006; Pande and Leis 1999).

Gastrointestinal hypo- or amotility in CIPO is demonstrated by oesophageal manometry, radiological investigations including barium meal examination and Gastrografin enemas (Chinn and Schuffler 1988). CT scan of the abdomen shows bowel distension without mechanical obstruction as does endoscopy of the gastrointestinal tract (Badari et al. 2012). Histopathological examination reveals inflammatory lymphocytic infiltrates in the myenteric plexus associated with Schwann cell proliferation and in most cases neuronal degeneration (Chinn and Schuffler 1988).

Paraneoplastic CIPO represents the minority of all cases with gastrointestinal dysmotility. A frequent cause is progressive systemic sclerosis followed by hollow visceral myopathy (Schuffler et al. 1981). Idiopathic cases of myenteric ganglionitis have been reported (Racalbuto et al. 2008). Familial cases with visceral myopathy associated with CIPO can occur (Sipponen et al. 2009). Amyloidosis may also present as CIPO (Wald et al. 1981). CIPO can develop as a late complication of radiotherapy (Conklin and Anuras 1981) and rarely in Chagas disease (Teixeira et al. 2006).

21.4.7 Lambert-Eaton Myasthenic Syndrome

Lambert-Eaton myasthenic syndrome (LEMS) is another classical PNS of the peripheral nervous systems. Paraneoplastic LEMS occurs approximately fivefold

less frequent than SSN and PCD (Giometto et al. 2010). Clinically, it is characterised by predominantly proximal muscle weakness, loss of tendon reflexes, mild to moderate ptosis and autonomic dysfunction, especially dryness of the mouth (O'Neill et al. 1988). In about 10 % of patients with paraneoplastic LEMS, cerebellar ataxia can be found (Titulaer et al. 2011b).

In approximately 50 % of patients, an underlying cancer, almost exclusively SCLC, is detected (Titulaer et al. 2011b). Typically, if present, an initially occult SCLC is diagnosed within the first 2 years after onset by LEMS when thorough tumour screenings including thoracic CT, bronchoscopy and even FDG-PET are applied. In rare cases, prostate cancer, then differentiated in a neuroendocrine phenotype, has been reported associated with LEMS (Tetu et al. 1989; Agarawal et al. 1995). In addition, single patients with thymomas have been reported (Morimoto et al. 2010; Lauritzen et al. 1980).

Antibodies against VGCC are present in 90 % of LEMS (Roberts et al. 1985). However, this finding does not discriminate between paraneoplastic and non-paraneoplastic cases. In approximately 70 % of patients with paraneoplastic LEMS, high titre-antibodies against SOX proteins can be found (Titulaer et al. 2009). Upon immunofluorescence on cerebellar tissue, this antibody corresponds to the anti-glial nuclear antigen (AGNA) pattern (Sabater et al. 2008). Anti-Hu antibodies are found in 30 % of patients with paraneoplastic LEMS (Titulaer et al. 2009). About 10–15 % of patients with LEMS are negative for antibodies against VGCC (Nakao et al. 2002). However, these sera induce similar effects in functional assays. This indicates the presence of antibodies interfering with presynaptic acetylcholine release that are currently undetectable by the available diagnostic tests (Nakao et al. 2002).

Electrophysiological tests can prove the clinically suspected diagnosis of LEMS. Nerve conduction studies show an abnormally low compound muscle action potential (CMAP) in patients with LEMS, which further decreases with low-frequency stimulation (Anonymous 2001). Although this decrement is not specific for LEMS, there is a substantial increment of the CMAP either postexercise or upon high-frequency stimulation (50 Hz) (Hatanaka and Oh 2008).

Using autopsy material, Fukuda et al. could show that in patients with cerebellar ataxia associated with LEMS, there is a marked decrease in cerebellar P/Q-type calcium channel expression (Fukuda et al. 2003).

When the diagnosis of LEMS is established based on clinical and electrophysiological findings, the main differential diagnosis to paraneoplastic LEMS is non-paraneoplastic LEMS. The Dutch-English LEMS Tumor Association Prediction (DELTA-P) score has been reported to accurately predict SCLC in LEMS. This score gives one point each of the following item, if they occur within 3 months after onset of LEMS: age ≥ 50 years, smoking at diagnosis, weight loss ≥ 5 %, bulbar involvement, erectile dysfunction in male patients and Karnofsky performance status lower than 70. Whereas a score of 0 and 1 is associated with low risk of an SCLC, a score of 3 and higher is almost invariably associated with paraneoplastic LEMS (Titulaer et al. 2011c). The presence of anti-SOX antibodies has a sensitivity of 67 % and a specificity of 95 % for LEMS with SCLC (Titulaer et al. 2009).

21.4.8 Nonclassical Paraneoplastic Syndromes

Some frequent neurological syndromes can be paraneoplastic in rare occasions. These include brainstem encephalitides, optic neuritis, retinal degeneration, stiff-person syndrome, myelitis including necrotising myelopathy, motor neuron diseases, diverse forms of neuropathy as well as myasthenia gravis and acquired neuromyotonia (Graus et al. 2004) and are described in this section.

Brainstem encephalitis can be observed as part of a generalised paraneoplastic encephalomyelitis but isolated paraneoplastic brainstem encephalitis can also occur in rare cases. Anti-Hu antibodies are associated with a predominantly medullary brainstem dysfunction (Saiz et al. 2009). These patients present with dysarthria, dysphagia and central hypoventilation. Facial, abducens and oculomotor nerve palsies and nystagmus occur frequently, sometimes progressing to complete gaze palsy. In 50 % of the patients, the disease starts with pontine or mesencephalic dysfunction but rapidly descends to the medulla. In contrast, brainstem encephalitis associated with anti-Ma2 antibodies predominantly affects upper brainstem functions. Patients suffer from vertical gaze palsy, and most of these patients have a combination of brainstem, diencephalic and limbic symptoms, sometimes leading to Parkinsonism, excessive daytime sleepiness and chorea (Dalmau et al. 2004). In cases with anti-Ri antibodies and brainstem dysfunction, eye movement disorders, dysphagia and ptosis have been described. Most patients also show postural instability (Sutton et al. 2002). Laryngospasm and/or jaw dystonia has been reported (Pittock et al. 2010). Interestingly, whereas cranial MRI in anti-Hu-associated brainstem encephalitis invariably shows no abnormalities (Saiz et al. 2009), the localisation of clinical brainstem involvement corresponds to T2 or FLAIR hyperintensities in patients with anti-Ma2 antibodies (Dalmau et al. 2004).

Paraneoplastic optic neuritis occurs most frequently in association with anti-CRMP5 antibodies (Cross et al. 2003). These patients also frequently show basal ganglia involvement upon imaging studies and autopsy, which is clinically evident as chorea (Vernino et al. 2002).

Paraneoplastic stiff-person syndrome (SPS) was first described by Moersch and Woltman in 1956. Patients present with chronic fluctuating truncal and proximal muscle rigidity and spasms (Moersch and Woltman 1956). The syndrome is caused by hyperexcitability of spinal motor neurons due to dysregulation of inhibitory GABAergic and glycinergic neurotransmission (Levy et al. 1999; Khasani et al. 2004). The combination of SPS and limbic encephalitis together with prominent myoclonus, hyperekplexia and oculomotor involvement has been referred to as progressive encephalomyelitis with rigidity and myoclonus (PERM) (Meinck et al. 1994). About 80 % of patients with SPS have high titres of anti-GAD antibodies (McKeon et al. 2012). There is an overlap of patients with anti-GAD antibodies and antibodies against the glycine-receptor $\alpha 1$ subunit (McKeon et al. 2013). Only in about 5 % of patients with SPS, a paraneoplastic origin can be assumed due to the coexistence of cancer. SPS is definitely paraneoplastic when anti-amphiphysin antibodies are detected, a finding that is usually associated with breast cancer (McKeon et al. 2012; Murinson and Guarnaccia 2008). Seronegative paraneoplastic SPS have

been reported in patients with Hodgkin lymphoma (McKeon et al. 2012). Less well-characterised antibodies associated with SPS include those against gephyrin (Butler et al. 2000) and antibodies against the potassium channel-associated protein DPPX, the latter in patients with a PERM-spectrum syndrome characterised by hyperekplexia and severe diarrhoea (Boronat et al. 2013).

Paraneoplastic myelitis is very rare. In a recent series of 31 cases of which 22 had onconeural antibodies, anti-amphiphysin and anti-CRMP5 antibodies (9 each) were the most common onconeural antibodies in isolated paraneoplastic myelitis (Flanagan et al. 2011). Aquaporin 4-antibodies can also occur in individual cases of paraneoplastic longitudinal extensive myelitis (LETM) (Pittock and Lennon 2008). Paraneoplastic necrotising myelopathy is a rare syndrome with rapidly progressive necrosis of the spinal cord, which clinically presents as ascending paraplegia followed by rapid deterioration and death (Ojeda 1984). This syndrome is usually not associated with onconeural antibodies (Graus et al. 2004).

Paraneoplastic retinal degeneration has also been recognised. The triad of photosensitivity, ring scotomas, visual field loss and attenuated retinal arteriole calibre has been reported as typical for this rare paraneoplastic disorder (Jacobson et al. 1990). Two different pathologies of the retina are distinguished: in melanoma-associated retinopathy, electrophysiological studies are consistent with a defect in intra-retinal transmission distal to the photoreceptors. Here, antibodies against bipolar retinal cells were reported, while the molecular mechanism remains unknown (Keltner et al. 2001; Weinstein et al. 1994). In contrast, in cancer-associated retinopathy, a degeneration of photoreceptor cells with limited signs of inflammation ensues (Buchanan et al. 1984). Here, antibodies against recoverin, a calcium-binding protein also expressed in underlying neoplasms, mostly SCLC (Polans et al. 1995), were identified (Polans et al. 1991). Retinitis can also occur in PNS associated with anti-CRMP5 antibodies but here visual loss is usually accompanied by additional neurological abnormalities (Cross et al. 2003).

There is no evidence for an increased frequency of motor neuron disease in cancer (Rosenfeld and Posner 1991). Generally, association of typical amyotrophic lateral sclerosis and cancer is most likely coincidental. However, a subset of patients with atypical MND suffer from paraneoplastic neurological syndromes. These include patients with subacutely progressive lower motor neuron disease, usually in association with anti-Hu antibodies and patients with isolated upper motor neuron disease, mostly associated with breast cancer (Forsyth et al. 1997). A recent survey supported the long acknowledged association of motor neuron disease with non-Hodgkin lymphomas; importantly none of the patients had inflammatory CSF changes, none showed improvement upon tumour treatment, and none had onconeural antibodies (Briani et al. 2011). Thus, a definite diagnosis of a PNS cannot be made in these cases.

Neuropathies are amongst the most frequent syndromes encountered by the clinical neurologist. The aetiologies encompass hereditary, metabolic, most frequently diabetic and inflammatory causes. Diverse forms of neuropathy including acute sensorimotor neuropathy mimicking Guillain-Barré syndrome (GBS), chronic inflammatory demyelinating polyradiculitis (CIDP), subacute to chronically progressive sensorimotor neuropathies, brachial plexusneuritis, vasculitic neuropathy

(Fig. 21.3) as well as dysautonomia can have a paraneoplastic origin (Koike et al. 2011). The detection of anti-Hu and anti-CRMP5 antibodies confirms the paraneoplastic origin in a subset of patients. Other subtypes that need to be mentioned specifically are neuropathies associated with monoclonal gammopathies of type IgM, mostly with antibodies against gangliosides or myelin-associated glycoprotein (Stork et al. 2014), which can also be considered as paraneoplastic. In POEMS syndrome, a monoclonal gammopathy, usually IgA lambda and a prominent increase in serum VEGF levels are confirmatory (Dispenzieri 2007).

Acquired neuromyotonia is a result of peripheral nerve hyperexcitability and leads to continuous involuntary muscle activity. Neuromyotonia and cramps-fasciculation syndrome represent a continuum (Hart et al. 2002). The likelihood that the acquired neuromyotonia is of paraneoplastic origin increases when the patient is older than 40 years and antibodies against voltage-gated potassium channels and acetylcholine receptors are found. The most common tumours are thymomas and SCLCs.

Myasthenia gravis, like LEMS, is a disorder with dysfunction of the neuromuscular junction. It is however initiated by antibodies against muscarinic acetylcholine receptors. Myasthenia gravis is paraneoplastic in a minority of cases and then associated with thymoma (Skeie and Romi 2008). The presence of anti-titin antibodies in patients with myasthenia gravis is associated with an underlying thymoma (Yamamoto et al. 2001).

21.5 Cerebrospinal Fluid Studies

As already discussed in the section regarding the pathophysiology of PNS, the PNS sensu stricto is an inflammatory disease of the nervous system. Thus, it is common practice in clinical neurology to use CSF analysis to detect or exclude inflammatory changes, thereby implying that the absence of inflammatory CSF changes makes a PNS unlikely or even excludes a inflammatory disease of the nervous system and thereby a PNS.

CSF analysis is an invaluable diagnostic tool for comprehensive differential diagnosis in suspected PNS. As described in the previous sections on each clinical syndrome, these comprise infectious, other autoimmune, neoplastic, toxic and hereditary causes. For example, CSF analysis might help to identify LE due to HSV reactivation by CSF-PCR and serology with determination of antigen-specific intrathecal antibody synthesis and *Listeria* species by CSF culture in brainstem encephalitis. In addition, in some autoimmune encephalitides, determination of antibodies in CSF has a higher sensitivity and specificity than serum testing only. In anti-NMDA receptor antibody encephalitis, CSF testing revealed anti-NMDA receptor antibodies in 16 % of cases in which serum was tested as negative (Gresa-Arribas et al. 2014). Thus, some very experienced laboratories use CSF only to screen for these kinds of antibodies in cases with LE (Jerome Honnorat, Lyon, personal communication), and some use serum and CSF in parallel (Josep Dalmau, Barcelona, personal communication). Furthermore, neurological signs or symptoms in some

cases of PNS, e.g. brainstem encephalitis or radiculitis, might be indistinguishable from those due to meningeosis carcinomatosa or leucemica or neurolymphomatosis. In these cases, even repeated CSF analysis including cytology or flow cytometry is advisable to exclude or confirm a direct effect of infiltrating neoplastic cells on the nervous system. In individual patients with PNS, the subacutely progressive course of the disease might lead to the differential diagnosis of CJD. Saiz et al. reported that the 14-3-3 protein in the CSF can be positive in 12.5 % of patients with PNS (Saiz et al. 1999). Thus, this marker is not reliable in distinguishing CJD from PNS. Taken together, CSF analysis is mandatory to clarify the differential diagnoses in cases with suspected PNS.

Whereas the specific findings to be expected upon CSF analysis in the diverse differential diagnoses of PNS will be covered in other chapters of this book, we will review here current knowledge about CSF findings in PNS. Even very early reports indicated that, in general, there are inflammatory CSF changes in PNS. However, since then there were only few systematic approaches to characterise the inflammatory CSF syndrome in PNS in detail. In these, methodological differences still leave room for ambiguity.

CSF results were reported in case series of PNS. An early series of patients with PCD with anti-Yo antibodies showed that 9 of 13 anti-Yo-positive cases had CSF abnormalities including mild lymphocytic pleocytosis and moderately elevated CSF protein, and the numbers of patients tested were very low however-positive oligoclonal bands (OCB) in CSF or elevated IgG (Anderson et al. 1988a). In a series of eight cases with paraneoplastic LE each with and without anti-Hu antibodies, the majority of cases had increased protein and CSF white blood cell (WBC) counts. OCBs were positive in five of six patients with anti-Hu antibodies (Alamowitch et al. 1997). In a larger series of patients with paraneoplastic LE, CSF showed inflammatory changes in 40/49 patients (24/47 increased total protein, 24/47 CSF pleocytosis, 15/15 increased IgG synthesis, 10/13 oligoclonal IgG) (Gultekin et al. 2000). In series of 19 patients with anti-Ri-associated PNS, less than 50 % had increased WBC count in the CSF or increased total protein but the absence or presence of OCB was not reported (Pittock et al. 2003). Lymphocytic pleocytosis, increased protein and isolated OCB in CSF were noted in most patients with paraneoplastic optic neuritis associated with anti-CRMP5 antibodies (Cross et al. 2003). In adult paraneoplastic OMS, 10/19 patients showed increased total protein or pleocytosis; two of these patients had oligoclonal IgG in the CSF (Anderson et al. 1988b). In most of these studies, the number of patients who neither had positive OCB, increased cell count or protein was not reported. Thus, the important question of the negative predictive value of normal CSF studies remains unanswered by these studies. In anti-Tr-associated PNS (mostly PCD), routine CSF analysis was normal in 9/22 patients; the remaining 13 patients had mild CSF pleocytosis with a median WBC count/ μl of 50 (range 14–150/ μl) (Bernal et al. 2003). Although as a group, anti-Tr-associated PNS had pleocytosis or CSF protein increase not different from other PNS, none of three patients tested had OCBs in the CSF (Psimaras et al. 2010). In 5 of 11 cases with Hodgkin lymphoma and PNS, CSF was reportedly normal (Briani et al. 2011). Although larger confirmatory studies are missing,

inflammatory CSF changes might be less frequent in PNS of the central nervous system associated with lymphomas than in PNS associated with other tumours. Correspondingly, in PNS of the peripheral nervous system, e.g. paraneoplastic demyelinating polyradiculoneuritis associated with lymphoma, CSF studies were normal except for increased total protein (Briani et al. 2011). However, in all these studies and many other reports about CSF abnormalities in patients with PNS, there are technical issues which limit comparability. It is often unknown which technique for the detection of OCB was used and whether serum and CSF were analysed in parallel. Thus, sensitivity between studies may vary considerably. Usually quantitative intrathecal IgG synthesis is reported as IgG index (e.g. (Cross et al. 2003)) or elevated CSF IgG (e.g. (Anderson et al. 1988a)) instead of the more accurate method developed by Reiber and Felgenhauer (1987).

The largest case series to date was published in 2010 by Psimaras et al. on behalf of the PNS Euronetwork (Psimaras et al. 2010). In this series, three basic values of CSF analysis were evaluated: WBC count, CSF protein levels and presence or absence of CSF OCB. Combining all these three values, abnormal CSF was found in 93 % of the patients; in 10 % of cases, the only abnormality was positive OCB. Pleocytosis, if present (39 %), was moderate, maximally 110 cells/ μ l, and CSF/blood-barrier dysfunction (>500 mg/l, present in 67 %) in some cases (13/281, 5 %) was substantial (>2,000 mg/l, maximally 4,000 mg/l). However, as it remained unclear whether the OCB detected in the CSF were actually isolated and not present in both serum and CSF, the value of this conclusion remains somewhat limited. Moreover, OCB were only analysed in 135/295 patients (46 %) and reported to be positive in 63 %. However, a small case series which definitely analysed OCB in serum and CSF in parallel led to similar results (10/18, 55 %: 3/5 patients with anti-Ri antibodies (Jarius et al. 2008), 3/3 anti-CV2 positive cases, 0/1 with anti-amphiphysin (Stich and Rauer 2007), 4/9 patients with anti-Yo-positive PCD (Stich et al. 2003)). In addition, the data published by Psimaras et al. indicated that lymphocytic pleocytosis as well as CSF/brain barrier dysfunction may subside during the course of the disease. Thus, normal results upon CSF analysis may be more often in the late stage of the disease (Psimaras et al. 2010). Counterintuitively, a higher cell count seems to be associated with a better prognosis regarding survival (Psimaras et al. 2010).

In the unpublished series of 13 patients with definite PNS, we cared for in the last years, using comprehensive CSF analysis, we observed similar results. In our patients, pleocytosis was present in 31 %. Upon routine cytology, lymphocytes dominated. Frequently, activated lymphocytes (up to 5 %) and plasma cells (up to 17 %) were observed. The CSF/serum albumin ratio (Q_{Alb}) was moderately increased in 69 %. The highest value was 27.9×10^{-3} in a case with SSN associated with uterus carcinoma. The majority of patients had isolated OCB in the CSF (69 %). Quantitative intrathecal IgG synthesis analysed by the formulas developed by Reiber occurred in 31 %; intrathecal IgA synthesis was not observed; only one patient had intrathecal IgM synthesis upon quantitative analysis (Reiber and Felgenhauer 1987). Three of 13 patients, a 63-year-old male with adenocarcinoma of the lung and motor neuron disease involving the upper and lower motor neuron,

a 60-year-old female with HL and motor neuropathy involving the cranial nerves and a 58-year-old male with squamous cell lung carcinoma, PCD and neuropathy, all without onconeural antibodies, had entirely normal CSF results. However, an isolated mild CSF/blood-barrier dysfunction was found in another patient. Thus, in our series strong indicators of an inflammatory disease, e.g. pleocytosis or intrathecal Ig synthesis, occurred in 69 % of patients only. In three of our patients with intrathecal IgG synthesis, the so-called MRZ reaction, a polyclonal increase of IgG against measles, rubella and varicella zoster, was tested. As in previous reports (Jarius et al. 2009), the MRZ reaction was negative in all patients.

Another question is whether CSF analysis can complement clinical monitoring for the efficacy of immunosuppressive and antitumour therapy. As indicated above, during the course of the disease, both pleocytosis and CSF/blood-brain barrier dysfunction may normalise without association of a better prognosis (Psimaras et al. 2010). We have followed a case with anti-Ri-positive myelitis without tumour and surprisingly good response to immunosuppression. In this case, over a period of more than 2 years, increases in the CSF/serum albumin ratio and CSF pleocytosis closely indicated relapses and both markers of inflammatory activity responded well to enforced immune suppression (Fig. 21.4) (Leypoldt et al. 2006). Thus, in individual cases, serial CSF analysis might be beneficial to guide therapeutic decisions (Fig. 21.5).

Importantly, CSF cannot only be used to detect and monitor inflammatory changes but also to look for the antibodies against onconeural antibodies that confirm the diagnosis of PNS (Graus et al. 2004). Already very early reports indicated that there is, at least in some cases, an intrathecal synthesis of onconeural antibodies as shown by Graus et al. in two patients with PCD and anti-Yo antibodies (Graus et al. 1988). A similar observation was published using quantitative western blotting in all of six patients harbouring anti-Ri antibodies in serum and CSF (Luque et al. 1991). Four of five patients with anti-Ma2 antibodies showed intrathecal synthesis (Voltz et al. 1999). These observations were supported by the detection of oligoclonal IgG specific for onconeural proteins in anti-Ri- (Jarius et al. 2008), anti-amphiphysin-, anti-CV2- (Stich and Rauer 2007), anti-Yo- (Stich et al. 2003) and anti-Hu-associated (Rauer and Kaiser 2000) PNS. Using ELISA to quantify antibody titres against onconeural antibodies, quantitative intrathecal synthesis of anti-Hu-IgG defined as an CSF/serum antibody index >1.5 was detected in 60 % of the patients (Rauer and Kaiser 2001). Presence or absence of intrathecal synthesis of anti-Hu antibodies in anti-Hu-positive PNS seemed to correlate with the presence or absence of oligoclonal IgG in the CSF (Rauer and Kaiser 2001). In the majority of patients (88 %) with primarily CNS involvement of the PNS and diverse antibodies, quantitative intrathecal synthesis was observed, while none of three patients with a PNS involving the peripheral nervous system had specific intrathecal antibody synthesis (Stich et al. 2007).

The 25-year experience of the laboratory at the MAYO Clinic in Rochester revealed that most cases of PNS with classical onconeural antibodies upon screening using indirect immunofluorescence show titres that are readily detectable in both serum and CSF (McKeon et al. 2011b). However, in 2 % of patients with

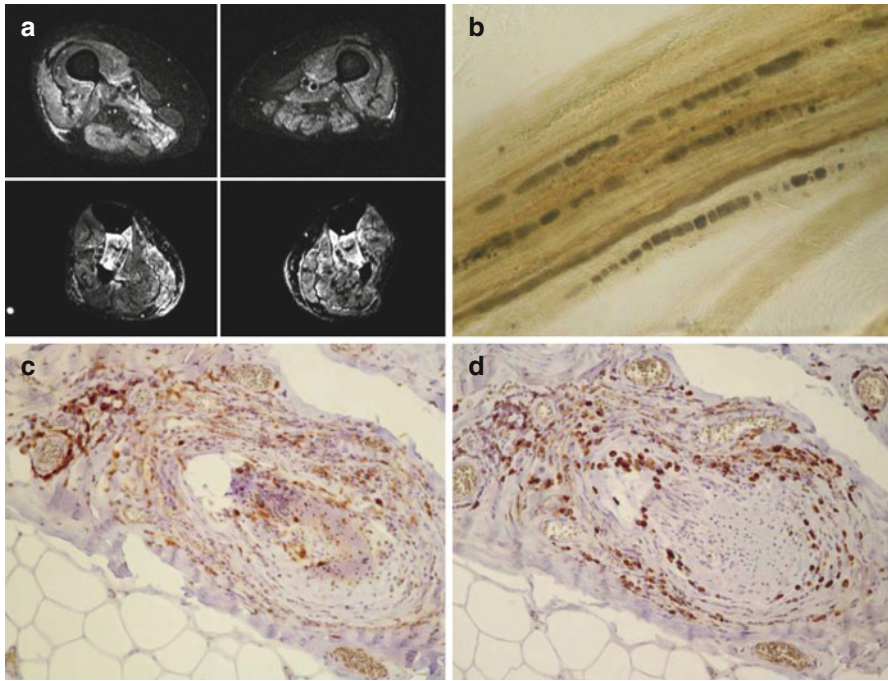


Fig. 21.4 Paraneoplastic vasculitic neuropathy associated with CRMP5- and amphiphysin antibodies and small-cell bladder carcinoma. The 74-year old patient with a present with chronically asymmetric painful sensorimotor neuropathy of the lower limbs. Four months before onset of symptoms a urothel carcinoma had been surgically removed. Cerebrospinal fluid (CSF) analysis showed lymphocytic pleocytosis (16 cells/ μ l), blood brain barrier dysfunction (Q_{Alb} 15.7 x 10^{-3}) and prominent intrathecal IgG synthesis (Q_{IgG} 22.6 x 10^{-3} , isolated oligoclonal bands in the CSF upon isoelectric focussing). **(a)** Muscle MRI showed scattered edema of legs muscles. **(b)** Nerve fiber teasing showed secondary myelin sheath degeneration. **(c/d)** Sural nerve biopsy showed vasculitis of the endoneurial vessels with lymphocytic infiltrates containing B cells **(c, anti-CD20)** and T cells **(d, anti-CD3)**. Antibody testing of the patients serum revealed high-titre anti-CRMP5 (1 : 245,760) and anti-amphiphysin antibodies (1 : 61.400) (Antibody testing was kindly performed by the Professor Vanda Lennon, Department of Laboratory Medicine and Pathology, Mayo Clinic, Rochester, MN, US; micrographs were provided by the courtesy of Professor Christian Hagel, Institute for Neuropathology, University Medical Center Hamburg-Eppendorf)

anti-Hu syndrome, antibodies were positive in either serum or CSF only. Seventeen per cent of patients with anti-Ri syndrome were positive in CSF only, while anti-Ri antibodies were detectable in serum only in 8 %. Six per cent of anti-Yo-positive patients were found to harbour anti-Yo antibodies in CSF only, while only 1 % were positive in serum. Three per cent of patients showed isolated anti-CRMP5 antibodies in either serum or CSF. Twenty per cent of patients with paired CSF and serum evaluated with positive results for anti-amphiphysin antibodies had detectable levels in CSF only, while 5 % were positive in serum only. Finally, two of 28 patients with anti-Tr-positive PNS showed anti-Tr antibodies in CSF but not in serum. Thus, in patients with classical well-characterised antibodies (including anti-Tr), detection

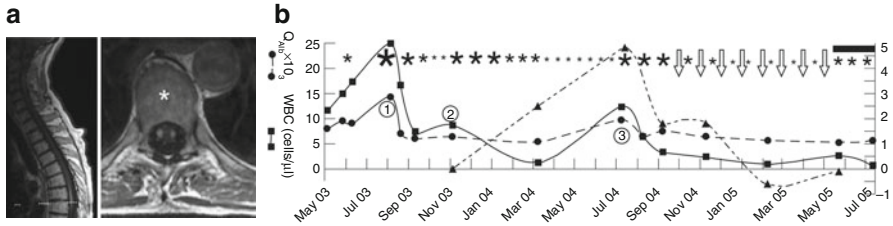


Fig. 21.5 Serial CSF analysis in a patient with anti-Ri-positive myelitis without tumour detected. The 65-year-old female presented with subacutely progressive spastic paraparesis due to myelitis demonstrated by MRI (a). Coronal and sagittal sections of gadolinium-enhanced T1-weighted spinal magnetic resonance image showing symmetrical contrast enhancement of the lateral aspects of the spinal cord. Asterisk indicates TH12. Dashed line indicates the level of axial section. (b) Clinical course including serial CSF analysis. Continuous line with closed boxes, white blood cells (WBCs (cells/μl), left y-axis, normal <5/μl); dashed line with filled circles, Q_{Alb} (CSF/serum albumin ratio $\times 10^3$, left y-axis, normal <8.4); dashed line with filled triangles, differences of left peroneal somatosensory-evoked potential (SEP) latencies compared with those from November 2003 (ms, right y-axis). Encircled numbers, numbered clinical relapses; open arrows, cyclophosphamide pulses; line of asterisks, steroid treatment, roughly corresponding in size of dose; filled line above asterisks, azathioprine treatment (Reprinted with permission from Leypoldt et al. (2006))

of antibodies in CSF only occurred twice as often as serum only positives (5 % vs. 2.5 %) (McKeon et al. 2011b).

In summary, in cases of suspected PNS, CSF analysis is (1) helpful in detecting CSF inflammation and (2) can complement serum testing for paraneoplastic antibodies. Unfortunately, commercially available tissues for immunofluorescence screening are mostly validated with serum only. Nevertheless, CSF testing for paraneoplastic antibodies should be performed in cases where the diagnosis of PNS is clinically suspected and serum antibody testing for onconeural antibodies remains negative.

21.6 Treatment

Treatment of paraneoplastic syndromes consists of tumour and/or immunosuppressive therapy. Prompt initiation of therapy is important. Unfortunately, most of the syndromes described in this chapter respond poorly to immunotherapy.

In large case series, elimination of tumour tissue in has been shown to be beneficial (Shams'ili et al. 2003; Graus et al. 2001; Candler et al. 2004). For example, in patients with a paraneoplastic encephalomyelitis associated with anti-Hu antibodies, tumour treatment was associated with recovery or stabilisation with an odds ratio of 4.56 (95 % confidence interval 1.62–12.86) (Graus et al. 2001). Patients with a paraneoplastic cerebellar degeneration with onconeural antibodies lived significantly longer if their tumour was treated (Shams'ili et al. 2003). Tumour therapy should be instituted according to current oncological guidelines; there is no evidence suggesting a different tumour treatment in paraneoplastic neurological

syndromes. However, in clinical oncology, the administration of aggressive chemotherapies is guided by the Karnofsky performance status. This measure can be quite low in patients with PNS due to neurological disturbances but not due to the cancer itself. This difference has to be thoroughly communicated by the treating neurologist. Efficacy of immunosuppression in paraneoplastic neurologic syndromes with onconeural antibodies is not supported by higher level evidence (Mason et al. 1997; Giometto et al. 2012; Greenlee 2013). However, expert opinion recommends immunosuppression in the absence of a detectable tumour or in combination with a tumour therapy in cases not improving or stabilising. No systematic studies exist concerning the type of immunosuppression. Mostly steroids, plasmapheresis, intravenous immunoglobulins (ivIG) or immunoadsorption in combination with cyclophosphamide-based immunosuppression are used. Biological therapies, e.g. rituximab, alemtuzumab and tocilizumab, can be considered but systematic evidence is lacking. Rituximab has been utilised with encouraging results in childhood opsoclonus-myoclonus syndrome (Battaglia et al. 2012). Immunosuppressants (azathioprine, methotrexate, cyclosporin A, tacrolimus, mycophenolate mofetil) are commonly used as steroid-sparing agents. In LEMS, treatment with steroids and azathioprine and in some cases immunoglobulins can be considered (Titulaer et al. 2011b; Keogh et al. 2011).

References

- Agarawal SK, Birch BR, Abercrombie GF (1995) Adenocarcinoma of the prostate and Eaton-Lambert syndrome. A previously unreported association. *Scand J Urol Nephrol* 29:351–353
- Ahmed MN, Carpenter S (1975) Autonomic neuropathy and carcinoma of the lung. *Can Med Assoc J* 113:410–412
- Alamowitch S, Graus F, Uchuya M et al (1997) Limbic encephalitis and small cell lung cancer. Clinical and immunological features. *Brain* 120(Pt 6):923–928
- Ali K, Amin R, Yoganathan KG et al (2013) Rapidly progressive cerebellar ataxia in West Wales. *BMJ Case Rep* 2013
- Altman AJ, Baehner RL (1976) Favorable prognosis for survival in children with coincident opsoclonus and neuroblastoma. *Cancer* 37:846–852
- Anderson NE, Rosenblum MK, Posner JB (1988a) Paraneoplastic cerebellar degeneration: clinical-immunological correlations. *Ann Neurol* 24:559–567
- Anderson NE, Budde-Steffen C, Rosenblum MK et al (1988b) Opsoclonus, myoclonus, ataxia, and encephalopathy in adults with cancer: a distinct paraneoplastic syndrome. *Medicine (Baltimore)* 67:100–109
- Anonymous (2001) Practice parameter for repetitive nerve stimulation and single fiber EMG evaluation of adults with suspected myasthenia gravis or Lambert-Eaton myasthenic syndrome: summary statement. *Muscle Nerve* 24:1236–1238
- Antunes NL, Khakoo Y, Matthay KK et al (2000) Antineuronal antibodies in patients with neuroblastoma and paraneoplastic opsoclonus-myoclonus. *J Pediatr Hematol Oncol* 22:315–320
- Armangue T, Titulaer MJ, Sabater L et al (2014) A novel treatment-responsive encephalitis with frequent opsoclonus and teratoma. *Ann Neurol* 75:435–441
- Badari A, Farolino D, Nasser E et al (2012) A novel approach to paraneoplastic intestinal pseudo-obstruction. *Support Care Cancer* 20:425–428
- Bataller L, Graus F, Saiz A et al (2001) Clinical outcome in adult onset idiopathic or paraneoplastic opsoclonus-myoclonus. *Brain* 124:437–443

- Bataller L, Rosenfeld MR, Graus F et al (2003) Autoantigen diversity in the opsoclonus-myoclonus syndrome. *Ann Neurol* 53:347–353
- Bataller L, Wade DF, Graus F et al (2004) Antibodies to Zic4 in paraneoplastic neurologic disorders and small-cell lung cancer. *Neurology* 62:778–782
- Bataller L, Kleopa KA, Wu GF et al (2007) Autoimmune limbic encephalitis in 39 patients: immunophenotypes and outcomes. *J Neurol Neurosurg Psychiatry* 78:381–385
- Battaglia T, De Grandis E, Mirabelli-Badenier M et al (2012) Response to rituximab in 3 children with opsoclonus-myoclonus syndrome resistant to conventional treatments. *Eur J Paediatr Neurol* 16:192–195
- Belcastro V, Piola M, Binda S et al (2014) Opsoclonus-myoclonus syndrome associated with human herpes virus-6 rhomboencephalitis. *J Neurol Sci* 341:165–166
- Bellur SN (1975) Opsoclonus: its clinical value. *Neurology* 25:502–507
- Bernal F, Shams'ili S, Rojas I et al (2003) Anti-Tr antibodies as markers of paraneoplastic cerebellar degeneration and Hodgkin's disease. *Neurology* 60:230–234
- Bhandari HS (2012) Presentation of opsoclonus myoclonus ataxia syndrome with glutamic acid decarboxylase antibodies. *BMJ Case Rep* 2012
- Bhanushali MJ, Kranick SM, Freeman AF et al (2013) Human herpes 6 virus encephalitis complicating allogeneic hematopoietic stem cell transplantation. *Neurology* 80:1494–1500
- BirluTiu V, BirluTiu RM (2014) Opsoclonus-myoclonus syndrome attributable to West Nile encephalitis: a case report. *J Med Case Rep* 8:232
- Blaes F, Fuhllhuber V, Korfei M et al (2005) Surface-binding autoantibodies to cerebellar neurons in opsoclonus syndrome. *Ann Neurol* 58:313–317
- Boltshauser E, Deonna T, Hirt HR (1979) Myoclonic encephalopathy of infants or "dancing eyes syndrome". Report of 7 cases with long-term follow-up and review of the literature (cases with and without neuroblastoma). *Helv Paediatr Acta* 34:119–133
- Boronat A, Sabater L, Saiz A et al (2011) GABA(B) receptor antibodies in limbic encephalitis and anti-GAD-associated neurologic disorders. *Neurology* 76:795–800
- Boronat A, Gelfand JM, Gresa-Arribas N et al (2013) Encephalitis and antibodies to dipeptidyl-peptidase-like protein-6, a subunit of Kv4.2 potassium channels. *Ann Neurol* 73:120–128
- Bozzola E, Bozzola M, Tozzi AE et al (2014) Acute cerebellitis in varicella: a ten year case series and systematic review of the literature. *Ital J Pediatr* 40:57
- Briani C, Vitaliani R, Grisold W et al (2011) Spectrum of paraneoplastic disease associated with lymphoma. *Neurology* 76:705–710
- Brunklaus A, Pohl K, Zuberi SM et al (2012) Investigating neuroblastoma in childhood opsoclonus-myoclonus syndrome. *Arch Dis Child* 97:461–463
- Buchanan TA, Gardiner TA, Archer DB (1984) An ultrastructural study of retinal photoreceptor degeneration associated with bronchial carcinoma. *Am J Ophthalmol* 97:277–287
- Butler MH, Hayashi A, Ohkoshi N et al (2000) Autoimmunity to gephyrin in Stiff-Man syndrome. *Neuron* 26:307–312
- Butterworth RF (1993) Pathophysiology of cerebellar dysfunction in the Wernicke-Korsakoff syndrome. *Can J Neurol Sci* 20(Suppl 3):S123–S126
- Camdessanche JP, Jousserand G, Ferraud K et al (2009) The pattern and diagnostic criteria of sensory neuronopathy: a case-control study. *Brain* 132:1723–1733
- Candler PM, Hart PE, Barnett M et al (2004) A follow up study of patients with paraneoplastic neurological disease in the United Kingdom. *J Neurol Neurosurg Psychiatry* 75:1411–1415
- Caviness JN, Forsyth PA, Layton DD et al (1995) The movement disorder of adult opsoclonus. *Mov Disord* 10:22–27
- Chinn JS, Schuffler MD (1988) Paraneoplastic visceral neuropathy as a cause of severe gastrointestinal motor dysfunction. *Gastroenterology* 95:1279–1286
- Choi KD, Kim JS, Park SH et al (2006) Cerebellar hypermetabolism in paraneoplastic cerebellar degeneration. *J Neurol Neurosurg Psychiatry* 77:525–528
- Conklin JL, Anuras S (1981) Radiation-induced recurrent intestinal pseudo-obstruction. *Am J Gastroenterol* 75:440–444

- Connolly AM, Pestronk A, Mehta S et al (1997) Serum autoantibodies in childhood opsoclonus-myoclonus syndrome: an analysis of antigenic targets in neural tissues. *J Pediatr* 130:878–884
- Corsellis JA, Goldberg GJ, Norton AR (1968) “Limbic encephalitis” and its association with carcinoma. *Brain* 91:481–496
- Cross SA, Salomao DR, Parisi JE et al (2003) Paraneoplastic autoimmune optic neuritis with retinitis defined by CRMP-5-IgG. *Ann Neurol* 54:38–50
- Cunningham J, Graus F, Anderson N et al (1986) Partial characterization of the Purkinje cell antigens in paraneoplastic cerebellar degeneration. *Neurology* 36:1163–1168
- Dalmau J, Furneaux HM, Gralla RJ et al (1990) Detection of the anti-Hu antibody in the serum of patients with small cell lung cancer—a quantitative western blot analysis. *Ann Neurol* 27:544–552
- Dalmau J, Graus F, Rosenblum MK et al (1992) Anti-Hu—associated paraneoplastic encephalomyelitis/sensory neuronopathy. A clinical study of 71 patients. *Medicine (Baltimore)* 71:59–72
- Dalmau J, Graus F, Cheung NK et al (1995) Major histocompatibility proteins, anti-Hu antibodies, and paraneoplastic encephalomyelitis in neuroblastoma and small cell lung cancer. *Cancer* 75:99–109
- Dalmau J, Graus F, Villarejo A et al (2004) Clinical analysis of anti-Ma2-associated encephalitis. *Brain* 127:1831–1844
- de Graaff E, Maat P, Hulsenboom E et al (2012) Identification of delta/notch-like epidermal growth factor-related receptor as the Tr antigen in paraneoplastic cerebellar degeneration. *Ann Neurol* 71:815–824
- DeFelipe-Mimbrera A, Masjuan J, Corral I et al (2014) Opsoclonus-myoclonus syndrome and limbic encephalitis associated with GABAB receptor antibodies in CSF. *J Neuroimmunol* 272:91–93
- Denny-Brown D (1948) Primary sensory neuropathy with muscular changes associated with carcinoma. *J Neurol Neurosurg Psychiatry* 11:73–87
- Dispenzieri A (2007) POEMS syndrome. *Blood Rev* 21:285–299
- Fisher PG, Wechsler DS, Singer HS (1994) Anti-Hu antibody in a neuroblastoma-associated paraneoplastic syndrome. *Pediatr Neurol* 10:309–312
- Flanagan EP, McKeon A, Lennon VA et al (2011) Paraneoplastic isolated myelopathy: clinical course and neuroimaging clues. *Neurology* 76:2089–2095
- Forsyth PA, Dalmau J, Graus F et al (1997) Motor neuron syndromes in cancer patients. *Ann Neurol* 41:722–730
- Fukuda T, Motomura M, Nakao Y et al (2003) Reduction of P/Q-type calcium channels in the postmortem cerebellum of paraneoplastic cerebellar degeneration with Lambert-Eaton myasthenic syndrome. *Ann Neurol* 53:21–28
- Gill JS, Windebank AJ (1998) Cisplatin-induced apoptosis in rat dorsal root ganglion neurons is associated with attempted entry into the cell cycle. *J Clin Invest* 101:2842–2850
- Giometto B, Marchiori GC, Nicolao P et al (1997) Sub-acute cerebellar degeneration with anti-Yo autoantibodies: immunohistochemical analysis of the immune reaction in the central nervous system. *Neuropathol Appl Neurobiol* 23:468–474
- Giometto B, Grisold W, Vitaliani R et al (2010) Paraneoplastic neurologic syndrome in the PNS Euronetwork database: a European study from 20 centers. *Arch Neurol* 67:330–335
- Giometto B, Vitaliani R, Lindeck-Pozza E et al (2012) Treatment for paraneoplastic neuropathies. *Cochrane Database Syst Rev* 12, CD007625
- Gohil A, Croffie JM, Fitzgerald JF et al (2001) Reversible intestinal pseudoobstruction associated with neural crest tumors. *J Pediatr Gastroenterol Nutr* 33:86–88
- Granerod J, Ambrose HE, Davies NW et al (2010) Causes of encephalitis and differences in their clinical presentations in England: a multicentre, population-based prospective study. *Lancet Infect Dis* 10:835–844
- Grau-Rivera O, Sanchez-Valle R, Saiz A et al (2014) Determination of neuronal antibodies in suspected and definite Creutzfeldt-Jakob disease. *JAMA Neurol* 71:74–78
- Graus F, Cordon-Cardo C, Posner JB (1985) Neuronal antinuclear antibody in sensory neuronopathy from lung cancer. *Neurology* 35:538–543

- Graus F, Elkon KB, Lloberes P et al (1987) Neuronal antinuclear antibody (anti-Hu) in paraneoplastic encephalomyelitis simulating acute polyneuritis. *Acta Neurol Scand* 75:249–252
- Graus F, Segurado OG, Tolosa E (1988) Selective concentration of anti-Purkinje cell antibody in the CSF of two patients with paraneoplastic cerebellar degeneration. *Acta Neurol Scand* 78:210–213
- Graus F, Dalmou J, Rene R et al (1997) Anti-Hu antibodies in patients with small-cell lung cancer: association with complete response to therapy and improved survival. *J Clin Oncol* 15:2866–2872
- Graus F, Keime-Guibert F, Rene R et al (2001) Anti-Hu-associated paraneoplastic encephalomyelitis: analysis of 200 patients. *Brain* 124:1138–1148
- Graus F, Lang B, Pozo-Rosich P et al (2002) P/Q type calcium-channel antibodies in paraneoplastic cerebellar degeneration with lung cancer. *Neurology* 59:764–766
- Graus F, Delattre JY, Antoine JC et al (2004) Recommended diagnostic criteria for paraneoplastic neurological syndromes. *J Neurol Neurosurg Psychiatry* 75:1135–1140
- Graus F, Arino H, Dalmau J (2014) Paraneoplastic neurological syndromes in Hodgkin and non-Hodgkin lymphomas. *Blood* 123:3230–3238
- Greene M, Lai Y, Baella N et al (2014) Antibodies to Delta/notch-like epidermal growth factor-related receptor in patients with anti-Tr, paraneoplastic cerebellar degeneration, and Hodgkin lymphoma. *JAMA Neurol* 71:1003–1008
- Greenlee JE (2013) Treatment of paraneoplastic cerebellar degeneration. *Curr Treat Options Neurol* 15:185–200
- Greenlee JE, Steffens JD, Clawson SA et al (2002) Anti-Hu antibodies in Merkel cell carcinoma. *Ann Neurol* 52:111–115
- Gresa-Arribas N, Titulaer MJ, Torrents A et al (2014) Antibody titres at diagnosis and during follow-up of anti-NMDA receptor encephalitis: a retrospective study. *Lancet Neurol* 13:167–177
- Griffin JW, Cornblath DR, Alexander E et al (1990) Ataxic sensory neuropathy and dorsal root ganglionitis associated with Sjogren's syndrome. *Ann Neurol* 27:304–315
- Gultekin SH, Rosenfeld MR, Voltz R et al (2000) Paraneoplastic limbic encephalitis: neurological symptoms, immunological findings and tumour association in 50 patients. *Brain* 123(Pt 7):1481–1494
- Hart IK, Maddison P, Newsom-Davis J et al (2002) Phenotypic variants of autoimmune peripheral nerve hyperexcitability. *Brain* 125:1887–1895
- Hatanaka Y, Oh SJ (2008) Ten-second exercise is superior to 30-second exercise for post-exercise facilitation in diagnosing Lambert-Eaton myasthenic syndrome. *Muscle Nerve* 37:572–575
- Hattori T, Hirayama K, Imai T et al (1988) Pontine lesion in opsoclonus-myoclonus syndrome shown by MRI. *J Neurol Neurosurg Psychiatry* 51:1572–1575
- Hayward K, Jeremy RJ, Jenkins S et al (2001) Long-term neurobehavioral outcomes in children with neuroblastoma and opsoclonus-myoclonus-ataxia syndrome: relationship to MRI findings and anti-neuronal antibodies. *J Pediatr* 139:552–559
- Henson RA, Hoffman HL, Urich H (1965) Encephalomyelitis with carcinoma. *Brain* 88:449–464
- Hoftberger R, Kovacs GG, Sabater L et al (2013) Protein kinase C gamma antibodies and paraneoplastic cerebellar degeneration. *J Neuroimmunol* 256:91–93
- Honnorat J, Antoine JC, Derrington E et al (1996) Antibodies to a subpopulation of glial cells and a 66 kDa developmental protein in patients with paraneoplastic neurological syndromes. *J Neurol Neurosurg Psychiatry* 61:270–278
- Honnorat J, Saiz A, Giometto B et al (2001) Cerebellar ataxia with anti-glutamic acid decarboxylase antibodies: study of 14 patients. *Arch Neurol* 58:225–230
- Ingenito GG, Berger JR, David NJ et al (1990) Limbic encephalitis associated with thymoma. *Neurology* 40:382
- Irani SR, Pettingill P, Kleopa KA et al (2012) Morvan syndrome: clinical and serological observations in 29 cases. *Ann Neurol* 72:241–255
- Jacobson DM, Thirkill CE, Tipping SJ (1990) A clinical triad to diagnose paraneoplastic retinopathy. *Ann Neurol* 28:162–167
- Jarius S, Stich O, Rasiyah C et al (2008) Qualitative evidence of Ri specific IgG-synthesis in the cerebrospinal fluid from patients with paraneoplastic neurological syndromes. *J Neurol Sci* 268:65–68

- Jarius S, Eichhorn P, Jacobi C et al (2009) The intrathecal, polyspecific antiviral immune response: specific for MS or a general marker of CNS autoimmunity? *J Neurol Sci* 280:98–100
- Jarius S, Martinez-Garcia P, Hernandez AL et al (2013) Two new cases of anti-Ca (anti-ARHGAP26/GRAF) autoantibody-associated cerebellar ataxia. *J Neuroinflammation* 10:7
- Jones HR Jr, Hedley-Whyte ET, Freidberg SR et al (1982) Primary cerebellopontine progressive multifocal leukoencephalopathy diagnosed premortem by cerebellar biopsy. *Ann Neurol* 11:199–202
- Keltner JL, Thirkill CE, Yip PT (2001) Clinical and immunologic characteristics of melanoma-associated retinopathy syndrome: eleven new cases and a review of 51 previously published cases. *J Neuroophthalmol* 21:173–187
- Keogh M, Sedehizadeh S, Maddison P (2011) Treatment for Lambert-Eaton myasthenic syndrome. *Cochrane Database Syst Rev* (2):CD003279
- Khasani S, Becker K, Meinck HM (2004) Hyperekplexia and stiff-man syndrome: abnormal brainstem reflexes suggest a physiological relationship. *J Neurol Neurosurg Psychiatry* 75:1265–1269
- Kim H, Lim Y, Kim KK (2009) Anti-ri-antibody-associated paraneoplastic syndrome in a man with breast cancer showing a reversible pontine lesion on MRI. *J Clin Neurol* 5:151–152
- Kimmel DW, O'Neill BP, Lennon VA (1988) Subacute sensory neuropathy associated with small cell lung carcinoma: diagnosis aided by autoimmune serology. *Mayo Clin Proc* 63:29–32
- Kinsbourne M (1962) Myoclonic encephalopathy of infants. *J Neurol Neurosurg Psychiatry* 25:271–276
- Klaas JP, Ahlskog JE, Pittock SJ et al (2012) Adult-onset opsoclonus-myoclonus syndrome. *Arch Neurol* 69:1598–1607
- Koike H, Tanaka F, Sobue G (2011) Paraneoplastic neuropathy: wide-ranging clinicopathological manifestations. *Curr Opin Neurol* 24:504–510
- Krarup-Hansen A, Helweg-Larsen S, Schmalbruch H et al (2007) Neuronal involvement in cisplatin neuropathy: prospective clinical and neurophysiological studies. *Brain* 130:1076–1088
- Kulling D, Reed CE, Verne GN et al (1997) Intestinal pseudo-obstruction as a paraneoplastic manifestation of malignant thymoma. *Am J Gastroenterol* 92:1564–1566
- Kurian M, Lalive PH, Dalmau JO et al (2010) Opsoclonus-myoclonus syndrome in anti-N-methyl-D-aspartate receptor encephalitis. *Arch Neurol* 67:118–121
- Lancaster E, Dalmau J (2012) Neuronal autoantigens–pathogenesis, associated disorders and antibody testing. *Nat Rev Neurol* 8:380–390
- Lancaster E, Martinez-Hernandez E, Titulaer MJ et al (2011) Antibodies to metabotropic glutamate receptor 5 in the Ophelia syndrome. *Neurology* 77:1698–1701
- Lauritzen M, Smith T, Fischer-Hansen B et al (1980) Eaton-Lambert syndrome and malignant thymoma. *Neurology* 30:634–638
- Lawn ND, Westmoreland BF, Kiely MJ et al (2003) Clinical, magnetic resonance imaging, and electroencephalographic findings in paraneoplastic limbic encephalitis. *Mayo Clin Proc* 78:1363–1368
- Lennon VA (1994) The case for a descriptive generic nomenclature: clarification of immunostaining criteria for PCA-1, ANNA-1, and ANNA-2 autoantibodies. *Neurology* 44:2412–2415
- Lennon VA, Sas DF, Busk MF et al (1991) Enteric neuronal autoantibodies in pseudoobstruction with small-cell lung carcinoma. *Gastroenterology* 100:137–142
- Levy LM, Dalakas MC, Floeter MK (1999) The stiff-person syndrome: an autoimmune disorder affecting neurotransmission of gamma-aminobutyric acid. *Ann Intern Med* 131:522–530
- Leypoldt F, Eichhorn P, Saager C et al (2006) Successful immunosuppressive treatment and long-term follow-up of anti-Ri-associated paraneoplastic myelitis. *J Neurol Neurosurg Psychiatry* 77:1199–1200
- Li J, Zhou DB (2013) New advances in the diagnosis and treatment of POEMS syndrome. *Br J Haematol* 161:303–315
- Lucchinetti CF, Kimmel DW, Lennon VA (1998) Paraneoplastic and oncologic profiles of patients seropositive for type 1 antineuronal nuclear autoantibodies. *Neurology* 50:652–657

- Luque FA, Furneaux HM, Ferziger R et al (1991) Anti-Ri: an antibody associated with paraneoplastic opsoclonus and breast cancer. *Ann Neurol* 29:241–251
- Mason WP, Graus F, Lang B et al (1997) Small-cell lung cancer, paraneoplastic cerebellar degeneration and the Lambert-Eaton myasthenic syndrome. *Brain* 120(Pt 8):1279–1300
- Maverakis E, Goodarzi H, Wehrli LN et al (2012) The etiology of paraneoplastic autoimmunity. *Clin Rev Allergy Immunol* 42:135–144
- McKeon A, Lennon VA, Lachance DH et al (2009) Ganglionic acetylcholine receptor autoantibody: oncological, neurological, and serological accompaniments. *Arch Neurol* 66:735–741
- McKeon A, Tracy JA, Pittock SJ et al (2011a) Purkinje cell cytoplasmic autoantibody type 1 accompaniments: the cerebellum and beyond. *Arch Neurol* 68:1282–1289
- McKeon A, Pittock SJ, Lennon VA (2011b) CSF complements serum for evaluating paraneoplastic antibodies and NMO-IgG. *Neurology* 76:1108–1110
- McKeon A, Robinson MT, McEvoy KM et al (2012) Stiff-man syndrome and variants: clinical course, treatments, and outcomes. *Arch Neurol* 69:230–238
- McKeon A, Martinez-Hernandez E, Lancaster E et al (2013) Glycine receptor autoimmune spectrum with stiff-man syndrome phenotype. *JAMA Neurol* 70:44–50
- Meinck HM, Ricker K, Hulser PJ et al (1994) Stiff man syndrome: clinical and laboratory findings in eight patients. *J Neurol* 241:157–166
- Moersch FP, Woltman HW (1956) Progressive fluctuating muscular rigidity and spasm (“stiff-man” syndrome); report of a case and some observations in 13 other cases. *Proc Staff Meet Mayo Clin* 31:421–427
- Molinuevo JL, Graus F, Serrano C et al (1998) Utility of anti-Hu antibodies in the diagnosis of paraneoplastic sensory neuropathy. *Ann Neurol* 44:976–980
- Monstad SE, Knudsen A, Salvesen HB et al (2009) Onconeural antibodies in sera from patients with various types of tumours. *Cancer Immunol Immunother* 58:1795–1800
- Morimoto M, Osaki T, Nagara Y et al (2010) Thymoma with Lambert-Eaton myasthenic syndrome. *Ann Thorac Surg* 89:2001–2003
- Murinson BB, Guarnaccia JB (2008) Stiff-person syndrome with amphiphysin antibodies: distinctive features of a rare disease. *Neurology* 71:1955–1958
- Musthafa CP, Moosa A, Chandrashekhara PA et al (2006) Intestinal pseudo-obstruction as initial presentation of thymoma. *Indian J Gastroenterol* 25:264–265
- Nakao YK, Motomura M, Fukudome T et al (2002) Seronegative Lambert-Eaton myasthenic syndrome: study of 110 Japanese patients. *Neurology* 59:1773–1775
- Newman NJ, Bell IR, McKee AC (1990) Paraneoplastic limbic encephalitis: neuropsychiatric presentation. *Biol Psychiatry* 27:529–542
- O’Neill JH, Murray NM, Newsom-Davis J (1988) The Lambert-Eaton myasthenic syndrome. A review of 50 cases. *Brain* 111(Pt 3):577–596
- Ojeda VJ (1984) Necrotizing myelopathy associated with malignancy. A clinicopathologic study of two cases and literature review. *Cancer* 53:1115–1123
- Ongerboer de Visser BW (1983) Anatomical and functional organization of reflexes involving the trigeminal system in man: jaw reflex, blink-reflex, corneal reflex and exteroceptive suppression. In: Desmedt JE (ed) *Motor control mechanisms in health and disease*. Raven Press, New York, pp 727–738
- Pande R, Leis AA (1999) Myasthenia gravis, thymoma, intestinal pseudo-obstruction, and neuronal nicotinic acetylcholine receptor antibody. *Muscle Nerve* 22:1600–1602
- Panegyres PK, Reading MC, Esiri MM (1993) The inflammatory reaction of paraneoplastic ganglionitis and encephalitis: an immunohistochemical study. *J Neurol* 240:93–97
- Pittock SJ, Lennon VA (2008) Aquaporin-4 autoantibodies in a paraneoplastic context. *Arch Neurol* 65:629–632
- Pittock SJ, Lucchinetti CF, Lennon VA (2003) Anti-neuronal nuclear autoantibody type 2: paraneoplastic accompaniments. *Ann Neurol* 53:580–587
- Pittock SJ, Parisi JE, McKeon A et al (2010) Paraneoplastic jaw dystonia and laryngospasm with antineuronal nuclear autoantibody type 2 (anti-Ri). *Arch Neurol* 67:1109–1115

- Polans AS, Buczylo J, Crabb J et al (1991) A photoreceptor calcium binding protein is recognized by autoantibodies obtained from patients with cancer-associated retinopathy. *J Cell Biol* 112:981–989
- Polans AS, Witkowska D, Haley TL et al (1995) Recoverin, a photoreceptor-specific calcium-binding protein, is expressed by the tumor of a patient with cancer-associated retinopathy. *Proc Natl Acad Sci U S A* 92:9176–9180
- Pranzatelli MR (1992) The neurobiology of the opsoclonus-myoclonus syndrome. *Clin Neuropharmacol* 15:186–228
- Psimaras D, Carpentier AF, Rossi C (2010) Cerebrospinal fluid study in paraneoplastic syndromes. *J Neurosurg Neurosurg Psychiatry* 81:42–45
- Racalbuto A, Magro G, Lanteri R et al (2008) Idiopathic myenteric ganglionitis underlying acute 'dramatic' intestinal pseudoobstruction: report of an exceptional case. *Case Rep Gastroenterol* 2:461–468
- Rakocevic G, Barohn R, McVey AL et al (2003) Myasthenia gravis, thymoma, and intestinal pseudo-obstruction: a case report and review. *J Clin Neuromuscul Dis* 5:93–95
- Rauer S, Kaiser R (2000) Demonstration of anti-HuD specific oligoclonal bands in the cerebrospinal fluid from patients with paraneoplastic neurological syndromes. Qualitative evidence of anti-HuD specific IgG-synthesis in the central nervous system. *J Neuroimmunol* 111:241–244
- Rauer S, Kaiser R (2001) Enzyme linked immunosorbent assay using recombinant HuD-autoantigen for serodiagnosis of paraneoplastic neurological syndromes. *Acta Neurol Scand* 103:248–254
- Reiber H, Felgenhauer K (1987) Protein transfer at the blood cerebrospinal fluid barrier and the quantitation of the humoral immune response within the central nervous system. *Clin Chim Acta* 163:319–328
- Roberts A, Perera S, Lang B et al (1985) Paraneoplastic myasthenic syndrome IgG inhibits 45Ca^{2+} flux in a human small cell carcinoma line. *Nature* 317:737–739
- Rosenfeld MR, Posner JB (1991) Paraneoplastic motor neuron disease. In: Rowland LP (ed) *Advances in neurology: amyotrophic lateral sclerosis and other motor neuron diseases*. Raven Press, New York, pp 445–459
- Rudnicki SA, Dalmau J (2005) Paraneoplastic syndromes of the peripheral nerves. *Curr Opin Neurol* 18:598–603
- Sabater L, Bataller L, Carpentier AF et al (2006) Protein kinase C gamma autoimmunity in paraneoplastic cerebellar degeneration and non-small-cell lung cancer. *J Neurol Neurosurg Psychiatry* 77:1359–1362
- Sabater L, Titulaer M, Saiz A et al (2008) SOX1 antibodies are markers of paraneoplastic Lambert-Eaton myasthenic syndrome. *Neurology* 70:924–928
- Saiz A, Graus F, Dalmau J et al (1999) Detection of 14-3-3 brain protein in the cerebrospinal fluid of patients with paraneoplastic neurological disorders. *Ann Neurol* 46:774–777
- Saiz A, Bruna J, Stourac P et al (2009) Anti-Hu-associated brainstem encephalitis. *J Neurol Neurosurg Psychiatry* 80:404–407
- Schuffler MD, Rohrmann CA, Chaffee RG et al (1981) Chronic intestinal pseudo-obstruction. A report of 27 cases and review of the literature. *Medicine (Baltimore)* 60:173–196
- Shams'ili S, Grefkens J, de Leeuw B et al (2003) Paraneoplastic cerebellar degeneration associated with antineuronal antibodies: analysis of 50 patients. *Brain* 126:1409–1418
- Sipponen T, Karikoski R, Nuutinen H et al (2009) Three-generation familial visceral myopathy with alpha-actin-positive inclusion bodies in intestinal smooth muscle. *J Clin Gastroenterol* 43:437–443
- Skeie GO, Romi F (2008) Paraneoplastic myasthenia gravis: immunological and clinical aspects. *Eur J Neurol* 15:1029–1033
- Smith JH, Dhamija R, Moseley BD et al (2011) N-methyl-D-aspartate receptor autoimmune encephalitis presenting with opsoclonus-myoclonus: treatment response to plasmapheresis. *Arch Neurol* 68:1069–1072
- Sommer C, Weishaupt A, Brinkhoff J et al (2005) Paraneoplastic stiff-person syndrome: passive transfer to rats by means of IgG antibodies to amphiphysin. *Lancet* 365:1406–1411

- Stich O, Rauer S (2007) Antigen-specific oligoclonal bands in cerebrospinal fluid and serum from patients with anti-amphiphysin- and anti-CV2/CRMP5 associated paraneoplastic neurological syndromes. *Eur J Neurol* 14:650–653
- Stich O, Graus F, Rasiah C et al (2003) Qualitative evidence of anti-Yo-specific intrathecal antibody synthesis in patients with paraneoplastic cerebellar degeneration. *J Neuroimmunol* 141:165–169
- Stich O, Jarius S, Kleer B et al (2007) Specific antibody index in cerebrospinal fluid from patients with central and peripheral paraneoplastic neurological syndromes. *J Neuroimmunol* 183:220–224
- Stork AC, van der Pol WL, Franssen H et al (2014) Clinical phenotype of patients with neuropathy associated with monoclonal gammopathy: a comparative study and a review of the literature. *J Neurol* 261:1398–1404
- Storstein A, Krossnes B, Vedeler CA (2006) Autopsy findings in the nervous system and ovarian tumour of two patients with paraneoplastic cerebellar degeneration. *Acta Neurol Scand Suppl* 183:69–70
- Sutton IJ, Barnett MH, Watson JD et al (2002) Paraneoplastic brainstem encephalitis and anti-Ri antibodies. *J Neurol* 249:1597–1598
- Tagliati M, Simpson D, Morgello S et al (1998) Cerebellar degeneration associated with human immunodeficiency virus infection. *Neurology* 50:244–251
- Talon P, Stoll C (1985) Opsomyoclonus syndrome in children. A new case. Review of the literature (110 cases). *Pediatric* 40:441–449
- Teixeira AR, Nitz N, Guimaro MC et al (2006) Chagas disease. *Postgrad Med J* 82:788–798
- Tetu B, Ro JY, Ayala AG et al (1989) Small cell carcinoma of prostate associated with myasthenic (Eaton-Lambert) syndrome. *Urology* 33:148–152
- Titulaer MJ, Klooster R, Potman M et al (2009) SOX antibodies in small-cell lung cancer and Lambert-Eaton myasthenic syndrome: frequency and relation with survival. *J Clin Oncol* 27:4260–4267
- Titulaer MJ, Soffiotti R, Dalmau J et al (2011a) Screening for tumours in paraneoplastic syndromes: report of an EFNS task force. *Eur J Neurol* 18:19–e13
- Titulaer MJ, Lang B, Verschuuren JJ (2011b) Lambert-Eaton myasthenic syndrome: from clinical characteristics to therapeutic strategies. *Lancet Neurol* 10:1098–1107
- Titulaer MJ, Maddison P, Sont JK et al (2011c) Clinical Dutch-English Lambert-Eaton Myasthenic syndrome (LEMS) tumor association prediction score accurately predicts small-cell lung cancer in the LEMS. *J Clin Oncol* 29:902–908
- Valls-Sole J, Graus F, Font J et al (1990) Normal proprioceptive trigeminal afferents in patients with Sjogren's syndrome and sensory neuronopathy. *Ann Neurol* 28:786–790
- Vernino S, Tuite P, Adler CH et al (2002) Paraneoplastic chorea associated with CRMP-5 neuronal antibody and lung carcinoma. *Ann Neurol* 51:625–630
- Voltz R, Gultekin SH, Rosenfeld MR et al (1999) A serologic marker of paraneoplastic limbic and brain-stem encephalitis in patients with testicular cancer. *N Engl J Med* 340:1788–1795
- Wald A, Kichler J, Mendelow H (1981) Amyloidosis and chronic intestinal pseudoobstruction. *Dig Dis Sci* 26:462–465
- Wanschitz J, Hainfellner JA, Kristoferitsch W et al (1997) Ganglionitis in paraneoplastic subacute sensory neuronopathy: a morphologic study. *Neurology* 49:1156–1159
- Weinstein JM, Kelman SE, Bresnick GH et al (1994) Paraneoplastic retinopathy associated with anti-retinal bipolar cell antibodies in cutaneous malignant melanoma. *Ophthalmology* 101:1236–1243
- Wildhaber B, Niggli F, Stallmach T et al (2002) Intestinal pseudoobstruction as a paraneoplastic syndrome in ganglioneuroblastoma. *Eur J Pediatr Surg* 12:429–431
- Yamamoto AM, Gajdos P, Eymard B et al (2001) Anti-titin antibodies in myasthenia gravis: tight association with thymoma and heterogeneity of nonthymoma patients. *Arch Neurol* 58:885–890
- Young CA, MacKenzie JM, Chadwick DW et al (1993) Opsoclonus-myoclonus syndrome: an autopsy study of three cases. *Eur J Med* 2:239–241
- Yu Z, Kryzer TJ, Griesmann GE et al (2001) CRMP-5 neuronal autoantibody: marker of lung cancer and thymoma-related autoimmunity. *Ann Neurol* 49:146–154