13 Paraneoplastic and Other Autoimmune Disorders

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Abbreviations

ACTH	Adrenocorticotrophic hormone
AEDs	Antiepileptic drugs
ALS	Amyotrophic lateral sclerosis
AMPA	α-Amino-3-hydroxy-5-methyl-4-isoxazolepropionic
ANNA-1	Antineuronal nuclear antibody-1
ANNA-2	Antineuronal nuclear antibody-2
ANNA-3	Antineuronal nuclear antibody-3
BDUMP	Bilateral diffuse uveal melanocytic proliferation
BRAO	Branch retinal artery occlusion
CAR	Cancer-associated retinopathy
CASPR2	Contactin-associated protein-like 2
CD	Cluster of differentiation
CLIPPERS	Chronic lymphocytic inflammation with pontine perivascular enhancement responsive to steroids
CRMP5	Collapsin response-mediator protein-5
CSF	Cerebral spinal fluid
CT	Computer tomography
DDPX	Dipeptidyl-peptidase-like protein-6
EEG	Electroencephalogram
EMG	Electromyogram
ERG	Electroretinogram
FDG-PET	Fluorodeoxyglucose-positron emission tomography
FLAIR	Fluid-attenuated inversion recovery
GABA	Gamma-aminobutyric acid
GABARAP	GABA receptor-associated protein
GAD	Glutamic acid decarboxylase
HSE	Herpes simplex encephalitis
IVIG	Intravenous immunoglobulin
LEMS	Lambert Eaton Myasthenic Syndrome
LGI1	Leucine-rich, glioma-inactivated protein 1
MAR	Melanoma-associated retinopathy
MG	Myasthenia gravis
MND	Motor neuron disease
MRI	Magnetic resonance imaging
mRS	Modified Rankin Scale
NAP	Neuronal adaptin-like protein
NCS	Nerve conduction studies
NMDAR	*N*-Methyl D-Aspartate receptor
NSCLC	Non-small-cell lung carcinoma
	opsoclonus myoclonus syndrome
OMS	Opsoclonus myoclonus syndrome

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PCA	Purkinje cell cytoplasmic antibody
PCD	Paraneoplastic cerebellar degeneration
PERM	Progressive encephalomyelitis with rigidity and myoclonus
PET/CT	Positron emission tomography/computed tomography
PND	Paraneoplastic neurologic disorder
PNMA	Paraneoplastic Ma antigens
POEMS	Polyneuropathy, organomegaly, endocrinopathy, monoclonal protein, skin changes
RNA	Ribonucleic acid
SCLC	Small-cell lung cancer
SPS	Stiff person syndrome
SREAT	Steroid responsive encephalopathy associated with autoimmune thyroiditis
SuS	Susac syndrome
VEGF	Vascular endothelial growth factor
VGCC	Voltage-gated calcium channel
VGKC	Voltage-gated potassium channel

Introduction

The term paraneoplastic neurologic disorder (PND) can describe any condition or syndrome for which there is a causal relationship between a malignant process that is distal from the inciting tumor and a systemic illness or collection of symptoms. In other words, these disorders are associated with tumors but are not caused by direct tumor invasion of the target tissue. Technically, PNDs include systemic conditions like Trousseau's syndrome, a malignancy-associated disorder characterized by migratory superficial thrombosis and thrombophlebitis. However, more commonly when this term is used, it describes a neurologic condition associated with malignancy. The underlying mechanism of PND is thought to be an exaggerated immune response against a neuronal protein expressed by the tumor [1, 2].

It is of foremost importance to note that the initial evaluation of a suspected PND starts with a detailed neurologic history and examination to characterize the syndrome. Not uncommonly, neurological manifestations present before the tumor has manifested [2].

Definition and Classifications

The list of paraneoplastic syndromes is rapidly growing as clinicians and scientists classify and associate antibodies with specific neurologic and non-neurologic symptoms and signs. The identification, classification, and treatment of paraneoplastic syndromes have become one of the most dynamic fields within neurology. Most neurologists who treat these conditions still divide them into two groups in an attempt to identify conditions that have stronger associations with malignancies, also known as "classical syndromes" prompting a more thorough evaluation for occult tumor, and those that have a more casual relationship with an underlying malignancy, also known as "nonclassical syndromes." These two groups can be further broken down based on location within the nervous system. Onconeuronal antibodies are directed against intracellular antigens.

Graus proposed diagnostic criteria that may help differentiate definite paraneoplastic disorders from possible paraneoplastic disorders [3] (see Fig. 13.1).

In addition to the distinction between classical and nonclassical paraneoplastic syndromes (Table 13.1), and possible versus definite paraneoplastic syndromes, a third method of classification of these syndromes exists that distinguishes clinical syndromes in relation to their antibodies. This system distinguishes syndromes with autoantibodies that are directed against intracellular proteins from those syndromes with autoantibodies opposed to proteins located on the cell surface (Tables 13.2 and 13.3). In general, this also separates non-paraneoplastic autoimmune encephalitis and other neurologic conditions from the classical paraneoplastic disorders. This antibody-based

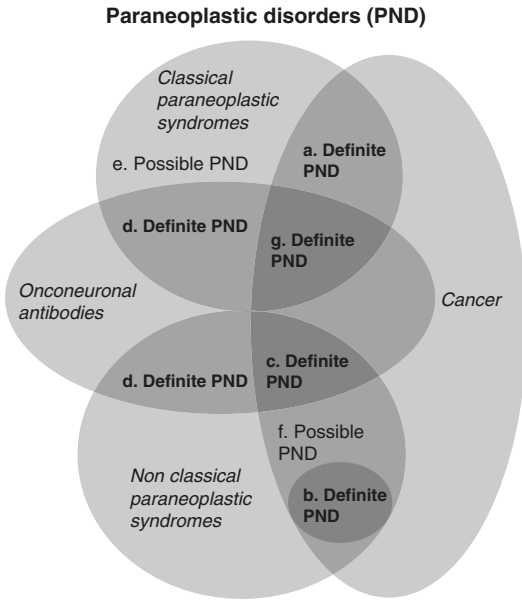

Fig. 13.1 Definite and possible paraneoplastic syndromes. (a) Classical syndrome and cancer that develops within 5 years of the diagnosis of the neurological disorder. (b) Nonclassical syndrome that resolves or improves after cancer treatment. (c) Nonclassical syndrome with onconeuronal antibodies and cancer that develops within 5 years of diagnosis of the neurological disorder. (d) Neurological syndrome (classical or not) with onconeural antibodies and no cancer. (e) Classical syndrome, no onconeuronal antibodies, no cancer but at high risk to have an underlying tumor. (f) Nonclassical syndrome, no onconeuronal antibodies (antibody and cancer present within 2 years of diagnosis). (g) A classical syndrome with onconeuronal antibodies and cancer

classification has important management and prognostic implications, as the response to immune therapy in patients with neuronal surface autoantibodies is far more favorable to immune therapy. This is not the case for paraneoplastic disorders caused by autoantibodies directed against intracellular proteins [1].

Clinical Features of Classical Syndromes

To better understand the paraneoplastic disorders, we will describe briefly the classical syndromes and specific antibody-associated syndromes. The reader must keep in mind that one classic paraneoplastic syndrome may be associated with multiple antibodies; for example, limbic encephalitis has been linked to 16 different antibodies (Tables 13.2 and 13.3) as of this publication. At the same time, one antibody can be associated with multiple paraneoplastic syndromes. The best example is the Anti-Hu antibody, which can present as a sensory neuronopathy, sensory-motor neuropathy, gastroparesis/autonomic involvement, limbic encephalitis, encephalomyelitis, and cerebellar degeneration (Table 13.2).

CNS Classical Syndromes

Paraneoplastic Limbic Encephalitis

Limbic encephalitis is the most common paraneoplastic syndrome. This classic syndrome may be paraneoplastic or idiopathic, depending on the type of associated antibodies. It presents as subacute psychiatric manifestations. Likely due to its temporal lobe and limbic structure involvement, this condition often presents with memory deficits, seizures, and behavioral abnormalities. Seizures that occur in limbic encephalitis may be difficult to control and often require multiple antiepileptic drugs (AEDs). Electroencephalograms (EEGs) in these patients can demonstrate diffuse or focal slowing and interictal discharges including sharp waves and spike waves.

Strict autoimmune encephalitis is more common than the classical paraneoplastic condition it resembles [4]. Although many of the antibodies that can cause these conditions can develop in association with an underlying malignancy, they can often be found in the absence of an associated cancer or mass lesion. These conditions may also occur in a wider range of patients including young adults and sometimes children. The antibodies associated with non-paraneoplastic autoimmune encephalitis tend to be cell surface antigens rather than intracellular antigens and thus may have a higher response rate to treatment than the classical PND counterparts. There are many different antibodies associated with limbic encephalitis, several of which will be discussed below.

Table 13.1 Classical and nonclassical paraneoplastic syndromes classified by location

	Classical[a]	Nonclassical[b]
Supra-tentorial brain	Encephalomyelitis Limbic encephalitis	Demyelinating encephalopathy Chorea Parkinsonism
Brainstem and cerebellum	Cerebellar degeneration Opsoclonus/myoclonus	Brainstem encephalitis
Cranial nerves	Cancer-associated retinopathy Melanoma-associated retinopathy	Optic neuropathy Bilateral diffuse uveal melanocytic proliferation (BDUMP)
Spinal cord	Subacute motor neuronopathy	Necrotizing myelopathy/neuromyelitis optica Inflammatory myelitis Motor neuron disease Stiff person syndrome
Dorsal root ganglia and peripheral nerves	Sensory neuronopathy Chronic gastrointestinal pseudo-obstruction Polyneuropathy, organomegaly, endocrinopathy, monoclonal protein, skin changes (POEMS)	Autonomic neuropathy Acute sensorimotor neuropathy Polyradiculopathy Brachial neuropathy Chronic sensorimotor neuropathy Neuromyotonia
Neuromuscular junction and muscles	Lambert Eaton Myasthenic Syndrome Dermatomyositis	Myasthenia gravis Polymyositis Necrotizing myopathy Myotonia

[a]Strongly associated with malignancy even if antibodies are negative
[b]Not always associated with cancer

Table 13.2 Antibodies against intracellular/cytoplasmic or nuclear antigens. Onconeuronal antibodies

Antibody	Target	Symptoms and disorders	Associated malignancies
Anti-Hu/ANNA-1 [72]	Hu family of RNA-binding proteins HuA, HuB, HuC, HuD	Sensory neuronopathy Cerebellar degeneration Limbic encephalitis Chronic gastrointestinal pseudoobstruction Lambert Eaton Myasthenic Syndrome (uncommon) Brainstem encephalitis Neuropathies Multifocal nervous system involvement	SCLC NSCLC Prostate Gastrointestinal Breast Bladder Pancreas Ovarian
Anti-Ri/ANNA-2	Ri family of RNA-binding proteins	Opsoclonus/myoclonus Lambert Eaton Myasthenic Syndrome (uncommon) Cerebellar ataxia Jaw dystonia Laryngospasm Cranial neuropathies Myelopathy	SCLC Breast NSCLC
ANNA-3 [110]	Unknown	Limbic encephalitis Cerebellar ataxia Sensorimotor neuropathy Myelopathy	SCLC
Anti-Yo (f-1)	Purkinje cells	Cerebellar degeneration	Gynecologic malignancy Endometrial, fallopian, ovarian Breast

Table 13.2 (continued)

Antibody	Target	Symptoms and disorders	Associated malignancies
Anti-PCA-2	Purkinje cells	Cerebellar degeneration Limbic encephalitis Brainstem encephalitis	SCLC
Anti-Ma	PNMA1-6	Limbic encephalitis Brainstem encephalitis	Lung GI Breast Germ cell Lymphoma Salivary gland
Anti-Ma2	PNMA1-6	Limbic encephalitis Cranial neuropathies Brainstem encephalitis	Testicular germ cell Other testicular tumors Lung cancer
Anti-CRMP5 [111]	Collapsin response-mediator protein 5	Lambert Eaton Myasthenic Syndrome Limbic encephalitis Opsoclonus myoclonus Stiff person syndrome Optic neuropathy Movement disorders (chorea) Ataxia Myelopathy	SCLC Thymoma
Anti-GAD65	Purkinje cell cytoplasm	Stiff person syndrome Limbic encephalopathy Cerebellar degeneration Epilepsy Cerebellar ataxia Dyskinesia	Renal cell carcinoma Hodgkin disease SCLC GI malignancies
Anti-amphiphysin	Amphiphysin I (synaptic vessel recycling)	Stiff person syndrome Limbic encephalitis	SCLC Breast NSCLC
Zic-4 [112]	Granule cell neurons in cerebellum	Cerebellar degeneration	SCLC
Sox1 (anti-glial nuclear antibody) [113]	SRY-like HMG box proteins (nuclei of Bergmann)	Cerebellar degeneration Lambert Eaton Myasthenic Syndrome Limbic encephalitis Sensorimotor neuropathy	SCLC
Anti-Tr	Purkinje cell	Cerebellar degeneration	Hodgkin Lymphoma
Anti-protein kinase C gamma [114]	Purkinje cell	Cerebellar degeneration	NSCLC
Anti-ubiquitin conjugating enzyme UBE2E1 [115]		Encephalomyelitis	SCLC
Anti-NB (beta-NAP) [35]	Purkinje cell	Cerebellar degeneration	Unknown
Anti-Carp VIII [18]	Purkinje cell	Cerebellar degeneration	Melanoma NSCLC Colon

ANNA antineuronal nuclear antibody, *RNA* ribonucleic acid, *SCLC* small-cell lung carcinoma, *NSCLC* non-small-cell lung carcinoma, *PCA* Purkinje cell cytoplasmic antibody, *PNMA* paraneoplastic Ma antigens, *NAP* neuronal adaptin-like protein

Table 13.3 Antibodies against neuronal surface antigens

Antibody	Target	Symptoms and disorder	Malignancies associated
Anti-NMDAR [13]	*N*-Methyl-D-aspartate receptor	Limbic encephalitis Encephalomyelitis Chorea/movement disorder Behavioral abnormalities	Ovarian teratoma Other ovarian pathology
LGI1 [19]	Leucine-rich, glioma-inactivated protein 1	Limbic encephalitis Morvan syndrome Faciobrachial dystonic seizures	
CASPR2 [61]	Contactin-associated protein-like 2	Limbic encephalitis Morvan syndrome	
AMPAR [18]	α-Amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid receptor	Limbic encephalitis Multifocal encephalomyelitis	Lung Thymoma Breast Ovarian
GABA-A-R [116]	GABA-A receptor-associated protein	Stiff person syndrome Limbic encephalitis	
GABA-B-R [117]	GABA-B receptor-associated protein	Limbic encephalitis	SCLC
MGluR5 [118]	Metabotropic glutamate receptors	Limbic encephalitis	Hodgkin lymphoma
mGluR1 [119]	Metabotropic glutamate receptors	Cerebellar degeneration	Hodgkin lymphoma
Homer 3 [18]	Post-synaptic scaffold protein	Cerebellar degeneration	SCLC
Dopamine D2 receptor	Dopamine D2 receptor	Encephalomyelitis	
Glycine receptor [55]	Glycine	Progressive encephalitis with rigidity and myoclonus	SCLC Breast cancer
DPPX [60]	Dipeptidyl-peptidase-like protein	Encephalopathy with muscle spasms, rigidity, myoclonus, hyperekplexia	B-cell neoplasms

N-Methyl D-Aspartate Receptor (NMDAR) Encephalitis

For many years, the only paraneoplastic syndromes associated with antibodies against ion channels or receptors were Lambert Eaton Myasthenic Syndrome (LEMS) and myasthenia gravis (MG). Paraneoplastic encephalitis was believed only to affect cytoplasmic or nuclear proteins and was characterized by poor response to treatment. In 2007, antibodies to the NMDAR subunit were described in 12 women with a distinct syndrome of psychiatric illness, seizures, dysautonomia, and hypoventilation associated with teratomas that responded well to immunotherapy [5]. Anti-NMDAR autoimmune encephalitis results in cross-linking and internalization of target receptors in neurons, resulting in impaired neurotransmission [6]. This was the first type of autoimmune encephalitis characterized molecularly, and subsequently a multitude of antibodies have been discovered [7]. Autoimmune encephalitis occurs at least ten times more common than all other synaptic antibody diseases combined [8], and is a more prevalent cause of encephalitis than any other single viral etiology [9]. These patients develop a predictable syndrome with progression of symptoms that resemble the clinical picture caused by noncompetitive agonists of NMDAR (such as phencyclidine or ketamine). The mild form of anti-NMDAR encephalitis can cause illusionary perceptions, ideas of reference, paranoia, and decreased executive function, which is characteristic of both disease onset, and months later, during recovery. More advanced disease can manifest as psychosis, agitation, stereotyped movements, repetitive motor behaviors, decreased responsiveness to pain, and memory disturbance. Very severe stages of anti-NMDAR encephalitis are characterized by dyskinesias, catatonia, autonomic dysfunction, hypoventila-

tion, and coma [10]. Triggers for the disease are tumors and viruses. In children, the clinical syndrome is different, characterized by behavioral changes and movement disorders (chorea, dyskinesia, or rigidity) rather than psychiatric manifestations. Seizures are common and can present at any stage of the disease [11].

Brain imaging typically shows contrast-enhancing lesions and fluid-attenuated inversion recovery (FLAIR) abnormalities in multiple regions but may have predominance in the hippocampus. Cerebral spinal fluid (CSF) may show lymphocytic pleocytosis and presence of oligoclonal bands [4]. EEGs can have a characteristic pattern called extreme delta brush [12].

Ovarian teratoma is concomitant in about 60% of cases in women aged 18 years or older [13]. NMDAR encephalitis has been reported in a variety of other tumors including teratomas outside the ovary, lymphomas, small-cell lung cancer (SCLC), and testicular germ cell tumors [14]. The frequency of an underlying teratoma is greater in females aged 12 years or older than in younger children and males (52% vs. 6%) [10]. Therefore, in females older than 12 years, the screening should be similar to that of paraneoplastic syndromes but screening of young children and males is unclear. Of note, approximately 20% of patients with herpes simplex encephalitis (HSE) develop antibodies against NMDAR [7].

In a large observational study, it was observed that immunotherapy and removal of any identified teratoma when applicable resulted in significant neurological recovery in about 81% of cases [12]. In this study, 91% of patients underwent first-line treatment with either high-dose steroids, intravenous immunoglobulin (IVIG), or plasma exchange alone or combined. Over 4 weeks, 53% of patients improved after first-line therapy and 97% of these patients had a good outcome of a modified Rankin Scale (mRS) 0–2 within 24 months. In the remainder of patients who continued to do poorly despite first-line therapy, 57% went on to receive second-line therapy which included rituximab, cyclophosphamide, or both. The patients receiving these interventions had better outcomes (in terms of mRS) than patients who received first-line treatment again or no additional treatment, indicating that patients unresponsive to initial agents may respond to rituximab or cyclophosphamide [12]. Immune therapy is combined with removal of any potential tumor, which decreases the probability of a relapse [15]. The only known predictors of a good outcome are lower severity of symptoms (lack of intensive care unit requirement) and early initiation of tumor removal when indicated [10].

New animal models have shown that the antibodies involved in autoimmune encephalitis are directly pathogenic [16]. Furthermore, administration of ephrin-B2 ligand antagonizes the pathogenic effects of NMDAR antibodies on memory and synaptic plasticity, promising a novel targeted therapy for NMDAR autoimmune encephalitis [17]. The combination of yearly discovery of new antibodies causing autoimmune encephalitis, historical and present misdiagnosis of these cases as psychiatric illness, and exciting new prospects for treatment make this branch of neurology an active field of research.

Anti-α-Amino-3-Hydroxy-5-Methyl-4-Isoxazolepropionic (AMPA) Receptor Encephalitis

Anti-AMPA receptor encephalitis occurs predominantly in women and in older populations as compared to NMDAR encephalitis. The median age for presentation is around 50–60 years [18]. The most common presentation is limbic encephalitis with seizures. Malignancy can be associated with this antibody in approximately 60% of cases, most commonly occurring in the lung, thymus, and breast [18].

LGI-1 (Leucine-Rich Glioma-Inactivated Protein 1) Encephalitis

LGI-1 antibody syndrome bears special mention because of its unusual presentation and often robust response to treatment with immunotherapy. LGI-1 stands for leucine-rich, glioma-inactivated protein 1, and it is a surface protein that was formerly believed to be associated with the voltage-gated potassium channel. About 50% of patients with LGI-1 syndrome present with facio-brachial dystonic seizures. Patients with these clinical epi-

sodes demonstrate brief, sudden onset dystonic posturing of the hand and ipsilateral face, often between 10 and 50 times per day [19, 20]. The same patient can have episodes independently on the right and left sides, and while clinical activity is quite stereotyped, the EEG often demonstrates no electrographic correlate. As LGI-1 antibody syndrome develops, cognitive and behavioral changes ensue, with memory loss, hallucinations, emotional incontinence, as well as temporal lobe seizures and sleep disorders such as insomnia. Hyponatremia is present in many patients. One small case series notes 4 of 10 patients with mild hyponatremia and 1 patient with severe hyponatremia to 115 at initial presentation [21]. Magnetic resonance imaging (MRI) may reveal FLAIR T2 hyperintensities in the medial temporal lobes and hippocampus [21]. Patients with this disorder often respond successfully to some combination of IVIG, corticosteroids, and/or plasmapheresis, but relapses can occur and repeat treatments are often necessary. LG1-1 syndrome is most commonly autoimmune, but rarely is associated with malignancies [21]. LGI-1 antibody syndrome was formerly thought to be limbic encephalitis due to voltage-gated potassium channel (VGKC) antibodies; in recent years, overlap has been found with another clinical syndrome, Morvan's syndrome, which is discussed below [22].

Antibody-Negative Limbic Encephalitis

There are cases of limbic encephalitis that do not have a known associated antibody that can be discovered. This is classified as antibody-negative limbic encephalitis. Graus et al. described 7% of 163 patients with a clinical and radiographic diagnosis of limbic encephalitis that do not have an identifiable causative antibody [23]. In almost half of these patients, a tumor was diagnosed at some point either prior to or subsequent to the diagnosis of limbic encephalitis. Despite the success in identifying new antibodies associated with autoimmune limbic encephalitis, there is still a subgroup of this condition where a causative antibody cannot be identified. In this small case series, a significant portion of patients responded to some immune suppression including steroids, IVIG, and rituximab [23].

Hashimoto's Encephalopathy

LGI-1 antibody syndrome bears similarity in presentation to Hashimoto's encephalopathy, an autoimmune encephalopathy known for its exquisite response to corticosteroids—also termed "steroid responsive encephalopathy associated with autoimmune thyroiditis (SREAT)." Patients with Hashimoto's encephalopathy can present with either subacute or acute-onset (stroke-like) symptoms including cognitive impairment, transient aphasia, psychotic symptoms, as well as tremulousness, myoclonus, ataxia, sleep abnormalities, and extrapyramidal signs. The cause of this disorder is not known, but patients can have high titers of anti-thyroid antibodies, including anti-thyroglobulin and anti-thyroperoxidase (nonspecific and fairly common antibodies that are not thought to be causative). Patients with this disorder can (but need not) have CSF pleocytosis or elevated protein; EEG with generalized or focal slowing and triphasic or epileptiform features; and brain MRI with diffuse atrophy and white matter T2 hyperintensities and/or ischemia. The diagnosis is made clinically based on a response to corticosteroids [24]. Hashimoto's encephalopathy is not a classic paraneoplastic limbic encephalitis but should be in the differential diagnosis for any patient presenting with limbic encephalitis symptoms.

Paraneoplastic Encephalomyelitis

This syndrome affects multiple regions of the central nervous system in addition to the limbic system. Often, there is cerebellar and brainstem involvement resulting in ataxia, vertigo, cranial nerve involvement, dysphagia, dysarthria, sleep disorders, and parkinsonism. It can also affect the spinal cord causing myelopathy. The most common malignancy associated is SCLC followed by testicular germ cell tumors [25]. The associated antibody is most commonly anti-Hu (associated with SCLC). This is followed by anti-Ma2 (associated with testicular germ cell tumors). Anti-collapsin response-mediator protein-5 (CRMP5), also known as CV2 antibodies, can also be associated with an encephalomyelitis but tends to involve additional symptoms including chorea and extrapyramidal symptoms as well as addi-

tional structures outside the brain and spinal cord including optic nerves and peripheral nerves [26]. There are a variety of other antibodies which can be associated with an encephalomyelitis including antibodies against amphiphysin, AMPA, gamma-aminobutyric acid (GABA), glutamic acid decarboxylase (GAD), and LGI-1. This condition, like most other paraneoplastic conditions, can occur in the absence of an identifiable antibody.

Paraneoplastic Cerebellar Degeneration

Paraneoplastic cerebellar degeneration (PCD) is a collection of disorders grouped together by common symptomatology. It presents most commonly in a rather stereotyped fashion. Symptoms often start with some mild dizziness and vertigo but progress to a more fulminant cerebellar syndrome. Patients very quickly develop diplopia, difficulty swallowing (often requiring parenteral enteric g-tube placement), dysarthria, severe ataxia (often wheelchair bound), nystagmus, gaze apraxia, hypophonia, nausea/vomiting, and tremors. This disease most commonly progresses in a subacute fashion over a few weeks but can progress much more rapidly [27, 28]. Untreated, after several months, symptoms may eventually stabilize. Some patients can develop the cerebellar affective syndrome which is associated with negativism [2].

In the acute setting, in most cases, brain imaging is normal; however, in some rare instances, there can be evidence of cerebellar inflammation. If patients survive long enough, cerebellar atrophy is often seen [29, 30]. There are a multitude of autoantibodies seen associated with this condition; however, the most common association is with Anti-Yo antibodies which is commonly seen in breast and gynecologic malignancies. The target of Anti-Yo antibodies is the Purkinje cell itself and on histologic evaluation of cerebellum in patients with anti-Yo-associated PCD, a complete loss of the Purkinje cell layer is often seen [31]. Anti-Hu antibodies can also be associated with PCD; however, often there is other associated neurologic conditions related to this autoantibody. A third antibody, Anti-Tr, is seen in association with Hodgkin disease [26]. Other antibodies associated with this syndrome include anti-GAD 65, anti-P/Q-type calcium channel antibody, and anti-mGluR1 antibody [32].

Due to its rapid, progressive nature, it is imperative to identify and treat this condition quickly. Often, symptoms of PCD are the presenting findings of a malignancy and many patients have limited-stage disease that would be amenable to anti-neoplastic therapies. This is particularly true with breast cancer patients [28]. However, this condition can progress to severe disability, but, in most cases, is not fatal.

Opsoclonus Myoclonus Syndrome

Opsoclonus myoclonus syndrome (OMS) can occur in either a paraneoplastic or a non-paraneoplastic form. In the non-paraneoplastic setting, it is most often related to a viral infection or is idiopathic in nature. Paraneoplastic OMS in children is almost exclusively associated with neuroblastomas [33]. In adults, OMS has been reported to be associated with breast cancer and small cell lung cancer [34]. Symptoms usually start with gait difficulty and falls. Ophthalmologic evaluation identifies opsoclonus, involuntary movements of the eyes in all directions. In most cases, the opsoclonus is associated with myoclonus.

A multitude of antibodies have been associated with patients who have this illness including Hu, Ri, Ma2, amphiphysin, CRMP5, Zic2, Yo, voltage-gated calcium channel (VGCC), and mitochondrial [35]. In adults, it is most commonly associated with Anti-Ri, Anti-Hu, and NMDA antibodies [34]. Many adults with this condition, however, have a non-paraneoplastic form [36].

First-line treatment in children often includes adrenocorticotrophic hormone (ACTH) or high-dose steroids. Rituximab has also been found to be beneficial [37].

Cancer-Associated and Related Autoimmune Retinopathies and Optic Neuropathies

There are a variety of retinopathies and optic neuropathies that are paraneoplastic in origin.

These disorders are quite uncommon and are caused by a variety of antibodies against retinal and optic nerve proteins. The typical presentation of these conditions is of subacute vision loss for which symptoms often predate the identification of a malignancy [38].

Anti-enolase antibodies are a more commonly associated antibody with CAR [39]. This antibody targets the alpha isoform of enolase which is present predominantly in retinal cells. There are several other less frequent antibodies which have been found to be pathologic in the development of cancer-associated antibody. These include glyceraldehyde-3-phosphate dehydrogenase antibodies, heat shock cognate protein 70 antibodies, Tubby-like protein antibodies, and anti-carbonic anhydrase II antibodies [40–43]. Electroretinogram (ERG) can be helpful in identifying these conditions. Abnormal ERGs which show a photoreceptor disorder should trigger a malignancy evaluation. This condition usually affects rods and cones together but can also affect them separately [44, 45]. ERGs can also be helpful in monitoring for progression of disease.

Melanoma-associated retinopathy (MAR) is an autoimmune retinopathy that is associated with melanoma. In this variant, it is much more common to present at the time of metastasis rather than at first diagnosis. Symptoms typically start with shimmering, flickering, and night blindness. Patients may also present with scotomas and may have significantly impaired visual acuity at the time of diagnosis. This condition is associated with a specific antibody: anti-bipolar cell antibodies. However, there are several other antibodies that may be associated with MAR. In addition, the ERG shows a characteristic pattern. This typically shows a reduction in the B wave amplitude and an abnormality in the "on" response to long flashes [44].

Paraneoplastic optic neuritis and neuropathies are extremely infrequent occurrences as either isolated conditions or in the setting of other more established disorders. Of the antibodies known to cause optic neuritis/neuropathy, anti-CRMP 5 (anti-CV2) is likely the most common. This antibody has been shown to cause both retinopathy and neuropathy. SCLC is the most common malignant etiology, although there are case reports in multiple myeloma and thyroid cancer [46–49]. Aside from the treatment of the suspected causal tumor, systemic immunosuppression and intravitreal corticosteroids have shown to improve vision in some patients [50].

Stiff Person Syndrome (SPS) and Progressive Encephalomyelitis with Rigidity and Myoclonus (PERM)

Stiff Person Syndrome (SPS) was first described in 1956 in a series of patients with progressive rigidity and painful spasms in axial and proximal muscles, and in particular, the paraspinal muscles [51]. Individuals with SPS typically present with progressive, regional, or generalized painful and rigid muscles; they are also prone to acute exacerbations of painful spasms, anxiety, and an exaggerated startle response. This startle response, as well as emotions like anxiety, anger, or fear, can in fact trigger painful spasms in the torso and limbs. These spasms can last hours or even days. During an exacerbation or with baseline muscle rigidity, the electromyography in SPS can detect hyperexcitable spinal motor neurons. Facial and jaw muscles are spared initially, although the face can be involved very late in the course of this disorder. The most common antibody associated with the condition is known as GAD65, which affects 60% of individuals with SPS [52]. GAD65 targets glutamic acid decarboxylase; the enzyme converts glutamate to GABA in the nervous system. Incidentally, this antibody is also frequently present in type I diabetics. In fact, 30% of patients with SPS also have insulin-dependent diabetes. Other diseases associated with GAD antibodies include autoimmune thyroiditis, cerebellar ataxia, and epilepsy. About 10–20% of individuals with SPS also have seizures [24].

SPS can be an autoimmune or paraneoplastic condition. Those with paraneoplastic SPS often have antibodies to amphiphysin; other autoantibodies implicated in the condition include gephyrin and GABA A receptor-associated protein (GABARAP) [53, 54].

A subpopulation of patients with SPS also have encephalomyelitis, which is considered a separate disorder known as progressive encephalomyelitis with rigidity and myoclonus (PERM), or "stiff person plus" disease [55]. This disorder is similar to SPS but more rapidly progressive (over weeks), and associated with other features including cognitive changes, seizures, diplopia, ophthalmoplegia, ptosis, dysphagia, ataxia, dysautonomia (including urinary and respiratory issues), hypersomnia, hyperhidrosis, myoclonus, itching, and panic attacks. PERM is associated with antibodies against glycine receptors (GlyR) present in serum and CSF [56, 57]. Both SPS and PERM have been described in patients with an underlying malignancy, without an underlying malignancy, and rarely following infection [58, 59].

Both paraneoplastic and autoimmune forms of SPS and PERM are typically treated with immune therapy, including but not limited to IVIG, plasmapheresis, corticosteroids, rituximab, and oral immunosuppressive medications. Symptoms can be managed with baclofen, benzodiazepines, and anticonvulsants [24].

PERM has also been associated with a novel antibody against dipeptidyl-peptidase-like protein-6 (DPP6 or DPPX). However, no malignancies have been associated with this antibody. DPPX is a regulatory subunit of the voltage-gated A-type Kv4.2 potassium channel complex expressed in neuronal dendrites and soma, which is critical for firing rates and back-propagations of action potentials into neuronal dendrites and cardiac rhythms. Since Kv4.2 channels are widespread in the nervous system, this manifests as a variety of symptoms besides PERM, which include encephalopathy involving cortex, cerebellum, and brainstem, weight loss, dysautonomia (temperature dysregulation, cardiac dysrhythmia), myelopathy, gastrointestinal dysmotility (diarrhea and gastroparesis), sleep disorders (insomnia, periodic limb movements, sleep apnea, hypersomnia), and psychiatric symptoms such as depression and psychosis [60].

Morvan's Syndrome

Morvan's syndrome is a rare disease, more common in older males, that is characterized by peripheral nerve hyperexcitability, autonomic instability, and neuropsychiatric manifestations [61]. Neurological symptoms and signs include insomnia, hallucinations, confusion, hyperhidrosis, pain, itching, muscle cramps, twitching (myokymia and/or myoclonus), and cerebellar features [62]. Morvan's syndrome can be autoimmune or paraneoplastic, often associated with small-cell lung cancer and thymoma (20–50% of cases) [24, 62]. Morvan's syndrome was formerly considered to be one of two paraneoplastic or autoimmune conditions associated with antibodies against voltage-gated potassium channels (VGKC antibodies), the other being a form of limbic encephalitis, with cognitive and behavioral changes and seizures [24, 63]. In fact, in recent years, two distinct antibodies have been identified with these two disorders: antibodies against contactin-associated protein-like 2 (CASPR2) are more frequently associated with the peripheral and autonomic hyperexcitability syndrome, while antibodies against (LGI-1) are more frequently associated with a type of limbic encephalitis, discussed elsewhere. However, substantial overlap can be found between these two antibodies and also with clinical syndromes [61]. In fact, among patients with CASPR2 antibodies, a limbic encephalitis presentation is in fact more common than Morvan's syndrome [61]. Some patients with Morvan's syndrome also co-express LGI-1 antibodies, and many co-express nonspecific antibodies to VGKC. However, there are many other patients with VGKC antibody positivity who have neither LGI-1 nor CASPR2 antibodies, and many more VGKC-positive patients are asymptomatic from a neurological standpoint, raising questions about the original designation of VGKC antibodies. LGI-1 and CASPR2 are both surface proteins, and treatment for associated clinical conditions can often include intravenous immunoglobulin, corticosteroids, and/or plasmapheresis. In patients with Morvan's syndrome who have thymoma, thymectomy is indicated and can resolve the neurological condition [61].

Peripheral Nervous System Classical Syndromes

Lambert Eaton Myasthenic Syndrome

Lambert Eaton Myasthenic Syndrome (LEMS) is a paraneoplastic syndrome that is most commonly associated with anti-VGCC in patients with SCLC. LEMS has associated specific electromyogram (EMG) and nerve conduction studies (NCS) findings which can aid in the diagnosis. This condition is discussed in detail elsewhere in this text.

Dermatomyositis

Dermatomyositis is an inflammatory myopathy that can present as a paraneoplastic syndrome in up to 15% of cases. It can be associated with a wide range of malignancies, particularly non-Hodgkin lymphoma, ovarian, and lung cancer [64]. Polymyositis and inclusion body myositis have low incidence of association with malignancies. This condition is discussed in detail elsewhere in this text.

Subacute Sensory Neuronopathy

The subacute sensory neuronopathy syndrome is one of the earliest described paraneoplastic syndromes. It can either be seen in isolated form or in association with an encephalomyelitis. The onset of this condition is usually quite rapid and associated with loss of sensation and paresthesias. Symptoms with sensory neuronopathy can sometimes begin in regions along the trunk as opposed to starting in the extremities and this pattern may indicate a search for a paraneoplastic syndrome. Pain may or may not be a significant symptom seen in this condition [35].

On electrodiagnostic testing, findings indicated a non-length-dependent nerve pattern of injury and is typically found in a widespread pattern. Since this is a dorsal root ganglion disorder, motor action potentials are usually unaffected. However, occasional motor abnormalities can be seen as well, indicating more widespread involvement of the peripheral nerves.

Most commonly, this condition is associated with the anti-Hu antibody in patients with SCLC. Often patients may progress to develop limbic encephalitis or other clinical symptoms associated with anti-Hu antibodies. Aside from SCLC, this condition can be associated with other malignancies like breast cancer or non-small-cell lung cancer [35].

Chronic Intestinal Pseudo-obstruction

This condition often presents with the symptoms of constipation and distension of the abdomen. It is caused by antibodies which react with the myenteric plexus and subsequent disruption of autonomic signaling to the gut. Most commonly, this occurs in relation to anti-Hu antibodies in association with SCLC [65]. Other antibodies may include anti-CRMP5 and a variety of voltage-gated channel antibodies.

POEMS (Polyneuropathy, Organomegaly, Endocrinopathy, Monoclonal Protein, and Skin Changes)

POEMS syndrome is a condition most associated with patients who have monoclonal gammopathy or frank multiple myeloma. The underlying cause of this condition is unknown and, like most of the conditions on this list, it may not necessarily be caused directly by antibodies produced by the immune system but potentially by overproduction of chemokines [66].

The International Myeloma Working Group has come up with specific criteria for the diagnosis of this syndrome. Both polyneuropathy and monoclonal plasma cell proliferative disorder are mandatory criteria for diagnosis. In addition, one major criterion is required which includes osteosclerotic lesions, Castleman's disease, or elevated serum or plasma vascular endothelial growth factor (VEGF) levels. One minor criterion must also be met which includes organomegaly, volume overload, endocrinopathy, skin changes, papilledema, or thrombocytosis/polycythemia. The neuropathy is usually the dominant symptom seen in this condition. Nerve injury tends to be more length-dependent and tends to be motor predominant. However, they may start with sensory symptoms [67].

There is no specific treatment recommended for this condition. Lenolidamide- and bortezomib-based treatments are favored by hematologists for treatment of the underlying condition due to limited toxicity with these therapies. Other approaches include hematopoietic stem cell transplantation [68]. From a symptom standpoint, there may be some benefit in using some anti-VEGF-related therapies like bevacizumab, but this has not been thoroughly evaluated [69].

Other Nonclassical Neurologic Paraneoplastic Symptoms

Outside of the classically defined paraneoplastic syndromes, there are a multitude of neurologic symptoms and syndromes which are thought to be paraneoplastic in origin. These can include simple neuropathies as well as paraneoplastic presentations of movement disorders like Parkinson disease and chorea, motor neuron diseases like amyotrophic lateral sclerosis (ALS), and myelopathies/myelitis.

Paraneoplastic movement disorders like chorea are some of the more common presentations of nonclassical autoimmune or paraneoplastic neurologic disorders. Choreiform movements can be found to be associated with multiple antibodies. Most commonly, this can involve anti-CRMP5 antibodies but can also occur with anti-Hu antibodies, GAD 65, CASPR2, and LGI1 antibodies. Paraneoplastic chorea is most often associated with SCLC, thymomas, non-Hodgkin lymphoma, and tonsillar squamous cell carcinoma. Non-paraneoplastic chorea can be associated with Lupus and antiphospholipid antibody syndrome [70, 71].

Isolated paraneoplastic myelopathies are uncommon; however, they may occur as part of a more extensive encephalomyelitis. There have been reports of transverse, necrotizing, and demyelinating myelitis. Anti-Hu antibodies are the most prevalent antibodies in paraneoplastic myelopathies [72]. Anti-CRMP5 antibodies have also been associated with necrotizing myelitis and bilateral optic neuritis in a neuromyelitis optica-like syndrome [73]. In many cases, paraneoplastic myelopathies present with longitudinally extensive abnormalities on MRI [74].

Many of the motor neuron diseases (MND) such as ALS typically occur in the same age group as patients prone to developing malignancy which can make the overall cause difficult to ascertain. In fact, there are many studies which question if there is a link between motor neuron disease and malignancy [75]. There is no definitive way to determine if a motor neuron disease is paraneoplastic in nature; however, if there is measurable improvement after treating the tumor itself, this would go against the natural course of any of the traditional MNDs. There are several cases reported in the literature involving lung and renal cell, that demonstrate either symptomatic improvement or complete recovery [76]. Breast cancer also seems to have some association with a motor neuron disease, potentially the primary lateral sclerosis variant [77]. Antibodies discovered in patients with an identified malignancy concurrent with a motor neuron-like syndrome include Anti-Hu, CRMP5, Yo, Spectrin, and Ma2 [78]; the later presenting with a progressive muscular atrophy-like syndrome [79]. In summary, there may be some rare individual cases of paraneoplastic MND but the vast majority of cases do not have a paraneoplastic origin.

Classification Based on Antibodies

In addition to classification of paraneoplastic disorders based on the disorder itself, these conditions can be classified based on the antibody causing the symptoms. Many paraneoplastic antibodies can present as several different disorders, both classical and nonclassical syndromes. The list of known antibodies identified seems to grow rapidly, not all of which are associated with malignancies. Antibodies can be grouped together into several larger categories including nuclear antibodies, cytoplasmic antibodies, and cell surface antibodies. Classifying these conditions based on the antibody itself may have some implications regarding treatment, since antibodies targeting cell surface antigens may have better

responses to immunosuppressants. Table 13.2 lists antibodies targeting antigens against intracellular, cytoplasmic, or nuclear antigens as well as known associated disorders and malignancies both common and uncommon that have been reported in these conditions. Table 13.3 lists cell surface antigens, their known symptoms, and associated malignancies.

Checkpoint Inhibitors and Risk of Paraneoplastic Neurological Disorders

Checkpoint inhibitors are immunomodulatory antibodies that have dramatically improved the prognosis of advanced malignancies; however, it is further recognized that these treatments can be associated with neurological complications and the development of autoimmunity including conditions like cerebellar ataxia, autoimmune retinopathy, autoimmune endocrinopathies, acute inflammatory demyelinating polyradiculoneuropathy, autoimmune myopathy, and myasthenia gravis [80]. Furthermore, patients treated with checkpoint inhibitors can also develop autoimmune encephalitis associated with multiple known antibodies including CRMP5 [81], NMDAR autoimmune encephalitis [82], and anti-Hu antibodies [83, 84]. It is thought that these treatments may predispose patients to the development of paraneoplastic disorders in some instances.

Diagnosis

Approaching the management of patients with suspected paraneoplastic disorders can also be a daunting task. The approach is different in patients who have a known malignancy compared to those without a known malignancy. Furthermore, patients with symptoms that fit within the classical paraneoplastic syndromes may alter the approach as well. By dividing patients with suspected PND into groups, the approach and the assessments necessary to manage these patients can be simplified.

In patients with no known cancer, an evaluation for evidence of a systemic malignancy should be performed after more common conditions are ruled out. Most often imaging of the nervous system is obtained to rule out structural or other causes of the presenting symptoms. Patients with classical paraneoplastic disorders, or in any patient who presents with unexplained subacute neurologic symptoms, warrant a systemic evaluation. Systemic imaging with a positron emission tomography/computed tomography or PET/CT or a CT of the chest, abdomen, and pelvis can identify asymptomatic malignancies. Of these modalities, a PET/CT scan could be of higher yield than a plain CT due to the often small nature of malignancies associated with PND. Other initial diagnostic testing depending on the clinical situation may include pelvic examination, mammogram, serum cancer markers, or a testicular ultrasound.

In patients with paraneoplastic encephalitis in many, but not all, cases, there are MRI findings that would be consistent with active inflammation. Mesiotemporal FLAIR hyperintensity ± enhancement may be present. Reports of up to 2/3 of patients show evidence of T2 or FLAIR hyperintensities in patients with anti-Hu-associated encephalitis [85, 86]. Brain fluorodeoxyglucose-positron emission tomography (FDG-PET) imaging may be helpful in identifying increased metabolism in MRI-negative encephalitis [87].

The next step in evaluation would typically include basic CSF evaluation including cell counts, IgG synthesis, oligoclonal bands, cytologic evaluation, and a guided search for paraneoplastic autoantibodies in the serum and CSF [88]. In one large series of limbic encephalitis, only 60% of patients had detectable autoantibodies [86]. If there are positive autoantibodies associated with common PND, this should prompt frequent surveillance of these patients for the development of new malignancies.

In patients with a known malignancy, as with those without known malignancy, a thorough search for alternate diagnoses which could explain their symptoms should be performed.

This would be followed by an evaluation of serum and CSF with basic studies and a targeted search for paraneoplastic autoantibodies based on the presenting symptoms.

Management

Due to the uncommon nature of PND and autoimmune encephalopathies, it is difficult to accrue evidence-based treatments for these conditions. Most data that have been gathered are in small case reports or case series. Despite the difficulty in collecting data regarding treatment of these uncommon conditions, there are some guidelines regarding management of PND that have been published [25].

The most effective method of treating these conditions is by initiating therapies directed toward the inciting tumor, which can include surgical resection, radiation, and chemotherapy. Resection is the most rapid way of removing the antigenic tissue, followed by radiation and then chemotherapy. If the source of the antigen is removed, it is possible to halt or slow progression of the condition. Immune modulatory therapies, including PD-1 inhibitors, could be used in certain scenarios but should be used cautiously as these medications tend to enhance the natural immune response to the tumor and thus theoretically may enhance the natural immune response to affected neural tissue as well [80, 89, 90].

Once a plan to address the primary malignancy is in place, treatments targeting the PND itself may be the next step. Frank immunosuppression or modulation of the immune system is generally thought to be the next step. These treatments generally start with high-dose methylprednisolone (1000 mg IV for 3–5 days). This can be used alone or in combination with other more acute therapies such as intravenous immunoglobulin or plasma exchange, particularly in more symptomatically severe or aggressive cases. Treatments such as these are usually initiated at initial diagnosis as more definitive, longer lasting treatments may take time to be arranged [91].

Cyclophosphamide is an immunosuppressant that can affect many facets of the immune system. There are several dosing regimens used in this setting, all of which are reported in small series. Dosing from a 1000 mg fixed dose to 750 mg/m^2 every 4 weeks split over 1–4 days per month has been used. This medication may be somewhat harsher than rituximab with regard to myelosuppression and systemic side effects. However, cyclophosphamide, a DNA alkylating agent, has a broader effect on the immune system than rituximab in that it can reduce proliferation of all cells within the immune system as opposed to rituximab which exerts its effects primarily on the B-cell population.

Rituximab, a CD20 monoclonal antibody, is primarily used in PND and other related disorders that are primarily antibody driven. In a single institutional study of patients with autoimmune limbic encephalopathy, the use of rituximab was found to be associated with more frequent functional improvement as compared to patients not treated with rituximab [92]. It has been shown to be beneficial in multiple paraneoplastic and other antibody-related conditions in small case reports including Morvan's syndrome, anti-NMDA receptor encephalitis, pediatric opsoclonus myoclonus syndrome, cancer-associated retinopathy, and paraneoplastic chronic intestinal pseudo-obstruction [93–95]. There are multiple regimens using rituximab, but most commonly, it is dosed at 375 mg/m^2 weekly over 4 weeks. There are even some regimens that rituximab is used in conjunction with cyclophosphamide [89, 96].

It is worth noting that the response to immune therapy in disorders mediated by antibodies targeting intracellular proteins may be less effective. These antibodies typically include most of the antibodies associated with the classical PNDs. Neurologic stability is often considered a favorable outcome in these conditions. Early diagnosis and immediate treatment may be key in preventing significant severe neurologic morbidity. On the contrary, synaptic and cell surface-mediated paraneoplastic syndromes have a better response to immune therapy. Many autoimmune encepha-

litidies, like anti-NMDA receptor encephalitis, are included in this category, which highlights the significant functional improvements seen with aggressive treatment.

Miscellaneous Neuroimmunologic Disorders

Outside of paraneoplastic and autoimmune neurologic disorders, there are several conditions or groups of conditions that affect the nervous system and have an inflammatory or immunologic component. These include conditions that may have a malignant component like several of the histiocytoses and conditions that are more strictly immunologic or inflammatory like Susac syndrome, or the chronic lymphocytic inflammation with pontine perivascular enhancement responsive to steroids syndrome (CLIPPERS). The rarity of many of these conditions limits the ability to better classify them and to develop appropriate therapies targeting them.

The histiocytoses make up a heterogenous group of conditions that involve abnormalities in the macrophage system. These conditions are split into two categories: Langerhans cell histiocytosis (LCH) which is more common, and the non-Langerhans cell histiocytoses, which include conditions like Erdheim-Chester disease (ECD), Rosai-Dorfman-Destombes disease (RDD), and other xanthogranulomas. None of these conditions are restricted to the CNS and in fact, most cases have manifestation outside of the brain or spinal cord. LCH rarely involves the CNS with the exception of supraoptic and periventricular nuclei which leads to diabetes insipidus. Outside of hypothalamic–pituitary axis, when it does involve the nervous system, it is typically due to CNS extension from lesions within the calvarium [97]. With the discovery of clonal BRAF V600E mutations with relatively common frequency in patients with ECD, the pathogenesis of this condition is more consistent with a malignant process [98]. This condition tends to cause enhancing lesions often in deep structures including the brainstem. To date, no recurrent mutation has been isolated in RDD and the most recent consensus guidelines favor an inflammatory origin for this condition [99].

Susac Syndrome

Susac is a rare disorder defined by the classical triad of encephalopathy, branch retinal artery occlusion (BRAO), and sensorineural hearing loss [100], although the majority of patients do not present with the complete clinical triad. It is more common in females than males. The encephalopathy is most often accompanied by headache, likely due to damage of leptomeningeal vessels. BRAO can affect the periphery and be silent but they can also affect the larger branches resulting in symptoms. Hearing loss, caused by occlusion of cochlear and semicircular canals arterioles, can be severely disabling and can be accompanied by severe tinnitus [101].

The etiology of this disorder is unclear but it is thought to be a microvascular autoimmune endotheliopathy that affects the central nervous system, retina, and inner ear. Brain biopsies show microvascular endothelium and vessel wall structure damage resulting in microinfarctions. Also, there is evidence of T-cell inflammation involving small–medium-sized vessels [102]. Several diagnostic tools are used. MRI always shows involvement of the corpus callosum (usually the central portion) with microinfarcts that can appear as “snowball” lesions. Central callosal holes are pathognomonic of the disease. Fluorescein angiography should be used to evaluate BRAO even in asymptomatic patients, and is characterized by multifocal fluorescence due to leakage of fluorescein in the damaged vessel. Yellow emboli (Gass plaques) can also be observed and represent the focal disturbance of the endothelium. Audiometric testing usually reveals affectation of the middle and lower frequencies first. CSF studies can show a lymphocytic pleocytosis with high protein. Angiography is without abnormality, as the vessels affected are too small to be detected [103]. Finally, antiendothelial antibodies can be of diagnostic significance [104].

The disease can relapse or remain continuously chronic. Encephalopathy and visual defects may remit but hearing loss is irreversible. It is important to diagnose this pathology early and treat aggressively to prevent relapses. Given the rarity of this disorder, there are no studies that show which are the best treatments. Immunotherapy is the mainstay of treatment and includes high-dose steroids, IVIG, cyclophosphamide, mycophenolate mofetil, infliximab, and rituximab [102, 103, 105].

Chronic Lymphocytic Inflammation with Pontine Perivascular Enhancement Responsive to Steroids Syndrome (CLIPPERS)

CLIPPERS is another rare disease affecting predominantly perivascular spaces in the pons with variable involvement of adjacent structures and striking response to steroids [106]. The mean age of onset is 50 years and there is a male predominance of 3:1 [107]. The classic presentation includes development of subacute gait ataxia and diplopia, dysarthria, dizziness, nystagmus, tremor, spasticity, cognitive impairment, and facial paresthesias; however, there are no clinical symptoms that are specific to this condition [108]. Brain MRI is the preferred diagnostic modality and it shows FLAIR hyperintensities in the perivascular spaces and white matter regions as well as a characteristic pattern of punctate and curvilinear enhancement, "peppering" of the pons and adjacent regions including the medulla, brachium pontis, and midbrain. The lesions are smaller and less frequent farther away from the pons. Other described symptoms include supratentorial lesions in addition to the typical infratentorial lesions [109]. Typical CSF findings can show normal or mildly elevated protein and rarely a lymphocytic pleocytosis. Brain biopsies demonstrate lymphocytic infiltrates in the white matter with perivascular predominance and markedly CD3 positive T-lymphocytes, mild B-lymphocytes, and moderate macrophage infiltrates [108]. Response to steroids is characteristic of the disease and often a helpful diagnostic tool. Steroid therapy is typically associated with improvement of symptoms and resolution of enhancing lesions [108], but patients often relapse when tapered off steroids. There are no guidelines for management due to the rarity of the disorder. Expert opinion suggests that response to treatment should be monitored periodically by clinical examination and serial brain MRI. Introduction of corticosteroid-sparing agents can be discussed in cases of relapse or due to steroid side effects. Agents to consider include methotrexate, cyclophosphamide, hydroxycloroquine, and azathioprine [107].

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