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# Paraneoplastic neurological syndromes: clinical presentations and management

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***Abstract*:** We provide an overview of the varied presentations of paraneoplastic neurological syndromes. We also review the onconeural antibodies and their particular oncological and neurological associations. Recognition of these syndromes and their oncological associations is crucial, as early diagnosis and management has been associated with better patient outcomes. Specific management strategies and prognosis vary widely depending on the underlying etiology. An understanding of the relevant clinical details, imaging findings, and other diagnostic information can help tailor treatment approaches. We provide an outline of the diagnostic evaluation and treatment of various paraneoplastic neurological disorders, presenting with central and/or peripheral nervous system involvement. We briefly discuss neurologic immune checkpoint inhibitor-related adverse events, which can occasionally present with paraneoplastic neurological syndrome phenotypes.

***Keywords:*** Paraneoplastic neurological syndrome, paraneoplastic neurological disorder, onconeural antibodies, immune checkpoint inhibitor

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## Introduction

Paraneoplastic neurological syndromes (PNS) are a group of neurological disorders not directly caused by cancer metastasis, side effects of cancer treatment, nutritional deficiencies, metabolic derangements, or coagulopathies. Rather, PNS are secondary to an immune response triggered by the underlying tumor which affects the central or peripheral nervous system.[1] These disorders can involve multiple levels of the neuraxis. The discovery of serological biomarkers with high specificities for an underlying malignancy[2] and/or clinical syndrome[3] have led to increased recognition and earlier diagnosis of these syndromes.[4] Timely diagnosis, prompt immunotherapy, and treatment of the underlying tumor are essential components of management of these cases. In this review article we discuss the clinical presentations of PNS as well as their serological and oncological associations. We also discuss our approach to immunotherapy for management of these cases.

## Epidemiology

Population-based epidemiology studies have highlighted that autoimmune disorders affecting the nervous system are not as rare as previously considered. A recent population-based study from Italy reported the incidence and prevalence of paraneoplastic disorders to be 0.89/100,000 person years and 4.4 per 100,000, respectively.[6] They utilized the paraneoplastic diagnostic criteria proposed in 2004 for case selection. Limbic encephalitis was the most common neurological phenotype, followed by paraneoplastic cerebellar degeneration and encephalomyelitis. Purkinje cell antibody type 1 (PCA-1, i.e. anti-Yo) and antineuronal nuclear antibody type 1 (ANNA-1, i.e. anti-Hu) were the most common onconeural antibodies in the studied population.

## Pathophysiology

PNS are triggered by an immune response against onconeural antigens expressed by the tumor that are also expressed in the nervous system.[4] These antigens are released after tumor-cell death and presented to the T cells by antigen-presenting cells in regional lymph nodes. This onconeural antigen-specific antibody or cell-mediated autoimmune response contributes to development of PNS.[7]

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The localization of antigenic target, to some extent, defines the disease pathobiology in the onconeural antibody-positive cases (Figure 1).[8] Syndromes associated with neural-specific antibodies targeting cell surface epitopes, such as gamma-aminobutyric acid (GABA)-B-receptor IgG, are considered to have an antibody-mediated pathogenesis, whereas patients with antibodies targeting intracellular epitopes such as PCA-1 IgG (i.e. anti-Yo IgG) have been demonstrated to have a cytotoxic T lymphocyte-mediated pathogenesis.[9]

### *Cell surface autoantigens*

Autoimmune syndromes associated with cell surface antibodies vary based on predominant IgG isotypes (IgG1–4). Aquaporin-4 autoimmunity, IgG1–3 autoantibodies cross-link with specific autoantigen, subsequently activating the complement system by forming the membrane attack complex (MAC) and leading to membrane damage of targeted cells.[10] Cross-linking, subsequent internalization, and antigen degradation are the mechanisms predominantly associated with α-amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid (AMPA) receptor(R), GABA-B-R, metabotropic glutamate receptor (mGlur)5-R, glycine receptor, and N-methyl-D-aspartate (NMDA)-receptor encephalitis. Among patients with leucine-rich glioma-inactivated protein (LGI1) or contactin-associated protein 2 (CASPR2) autoimmunity, IgG4 is the predominant subtype. IgG4 are functionally monovalent and cannot activate complement. LGI1 and CASPR2 antibodies have been demonstrated to act by disruption of protein–protein interaction by IgG4 autoantibodies.[11]

### *Intracellular autoantigens*

In contrast, antibodies targeting intracellular neural antigens are biomarkers of likely effector T-cell-mediated disease. Intracellular proteins are degraded by the proteasome to antigenic peptides and presented on the cell surface complex by major histocompatibility complex type 1 (MHC1) molecules.[10] The expression of MHC1 molecules on the neural surface may potentially be upregulated in the paraneoplastic setting by release of various cytokines such as interferon-γ, making them susceptible to autoantigen-specific cytotoxic T-cell response.[4]

### *Autoantibody testing and interpretation*

With growing recognition of PNS and utilization of onconeural antibody testing, the importance of recognizing the limitations of tests utilized becomes more apparent.[12] For most reference or commercial laboratories, clinical specificity should be the primary concern. This is because a false-positive neural antibody result can lead to potentially hazardous immunotherapy administration, repeated unnecessary malignancy screenings, and missed treatable alternative diagnoses.[13] Use of commercial immunoblots/immunodots as the only assay has been shown to generate higher false-negative and false-positive results.[14–16] Therefore, many referral neuroimmunology laboratories continue to utilize tissue-based immunofluorescence assays for screening of onconeural antibodies (Figure 2), and subsequent confirmation of these results with western blots or cell-based assays. For some onconeural antibodies such as Ma2 IgG, a combination of two independent recombinant protein based assays (such as commercial dot blot and in-house cell-based assays[17] or two independent commercial assays[18]) has also demonstrated higher clinical specificity.

Some onconeural antibodies like SOX1 and ANNA1 can occur in cancer patients without a PNS.[19–21] Therefore atypical clinical presentations among seropositive patients with underlying malignancy should lead to consideration and evaluation of alternative etiologies for neurological presentations as well.

## Clinical presentations

In 2004, a team of experts in the field of paraneoplastic neurological autoimmunity (Paraneoplastic Neurological Syndrome Euronetwork) formulated consensus criteria for PNS.[22] The diagnostic criteria had “definite PNS” and “possible PNS” subcategories (Table 1). These distinctions were made considering the specificity of the neurological syndrome, the onconeural antibody positivity, and the presence or absence of underlying malignancy. As per the expert consensus, certain clinical presentations were considered as “classical paraneoplastic phenotypes”: paraneoplastic encephalomyelitis, paraneoplastic limbic encephalitis, paraneoplastic cerebellar degeneration, paraneoplastic subacute sensory neuronopathy, and chronic gastrointestinal pseudo-obstruction.[22] Furthermore, certain neural-specific antibodies

**Table 1.** Classic and non-classic syndromes, and recommended 2004 diagnostic criteria for paraneoplastic neurological syndrome as per Paraneoplastic Neurological Syndrome Euronetwork.

| **Classic and non-classic syndromes consensus criteria** | **Definite Paraneoplastic Neurologic Syndrome criteria** |
|---|---|
| **Classic syndromes** | 1. A classical syndrome and cancer that develops within five years of the diagnosis of the neurological disorder. |
| 1. Limbic encephalitis | 2. A non-classical syndrome that resolves or significantly improves after cancer treatment without concomitant immunotherapy provided that the syndrome is not susceptible to spontaneous remission. |
| 2. Subacute sensory neuronopathy | 3. A non-classical syndrome with onconeural antibodies (well characterized or not) and cancer that develops within five years of the diagnosis of the neurological disorder. |
| 3. Subacute cerebellar degeneration | 4. A neurological syndrome (classical or not) with well-characterized onconeural antibodies (ANNA-1, PCA-1, ANNA-2, CRMP5, Ma2, Amphiphysin), and no cancer. |
| 4. Encephalomyelitis | **Possible Paraneoplastic Neurologic Syndrome criteria** |
| 5. Opsoclonus–myoclonus syndrome | 1. A classical syndrome, no onconeural antibodies, no cancer but at high risk to have an underlying tumor. |
| 6. Lambert–Eaton Myasthenic syndrome | 2. A neurological syndrome (classical or not) with partially characterized onconeural antibodies and no cancer. |
| 7. Chronic gastrointestinal pseudo-obstruction | 3. A non-classical syndrome, no onconeural antibodies, and cancer present within two years of diagnosis. |
| 8. Dermatomyositis | |
| **Non-classic syndromes**[a] | |
| 1. Brainstem encephalitis | |
| 2. Optic neuritis | |
| 3. Stiff person syndrome | |
| 4. Acquired Neuromyotonia | |
| 5. Motor neuron disease | |
| 6. Acute necrotising myopathy | |
| 7. Myasthenia gravis | |
| 8. Acute/subacute sensorimotor neuropathy | |
| 9. Acute dysautonomia | |

[a]list of non-classical syndromes or intermediate-risk phenotypes has changed considerably over the last few years, ANNA-1, anti-neuronal nuclear antibody type-1, ANNA-2, anti-neuronal nuclear antibody type-2, PCA-1, Purkinje cell antibody type-1, CRMP5 collapsin response-mediator protein-5.

were classified as classic or partially characterized onconeural antibodies. The list of onconeural antibodies has grown considerably with identification of many new autoantibody biomarkers in the last decade (Table 2). Of note, these diagnostic criteria may require further updates to reflect growing onconeural antibody profiles and description of new PNS-specific phenotypes. Clinical recognition of these syndromes and associated neural-specific autoantibodies may aid in early diagnosis and management of neurological autoimmunity but also detection of underlying tumor.

**Table 2.** Classic and novel antibodies with strong (>70%) oncological association.

| Antibody | Antigen target location | Common neurological presentations | Cancer association | Antibody detection methodology |
|---|---|---|---|---|
| ANNA-1 (i.e. anti-Hu) (Graus *et al.*; Lucchinetti *et al.*; Keime-Guibert *et al.*)[23–25] | Intracellular | Sensory neuronopathy, gastroparesis, limbic encephalitis, encephalomyelitis | Small-cell lung cancer | Tissue-based IFA, immunoblot, western blot |
| PCA-1 (i.e. anti-Yo) (Peterson *et al.*; Plantone *et al.*)[26,27] | Intracellular | Paraneoplastic cerebellar degeneration | Gynecological malignancies including (ovarian, uterine and breast adenocarcinoma) | Tissue-based IFA, immunoblot, western blot |
| CRMP5 (i.e. anti-CV2) (Yu *et al.*; Dubey *et al.)*[28,29] | Intracellular | Polyradiculoneuropathy, retinopathy, myelopathy, limbic encephalitis, cerebellar ataxia | Small-cell lung cancer, thymoma | Tissue-based IFA, immunoblot, western blot |
| ANNA-2 (i.e. anti-Ri) (Simard *et al.*; Pittock *et al.*)[30,31] | Intracellular | Rhombencephalitis, myoclonus, dystonia, parkinsonism | Breast adenocarcinoma, small-cell lung cancer | Tissue-based IFA, immunoblot, western blot |
| Ma2 (Dalmau *et al.*; Ortega Suero *et al.*)[32,33] | Intracellular | Limbic encephalitis, diencephalic encephalitis, rhombencephalitis | Testicular germ cell tumors, non-small-cell lung cancer (especially with co-existing Ma1 IgG seropositivity) | Tissue-based IFA, Immunoblot, CBA |
| Amphiphysin (De Camilli *et al.*; McKeon *et al.*)[34,35] | Intracellular antigen, but transiently expressed on the cell surface | SPSD, limbic encephalitis, polyradiculoneuropathy, myelopathy | Breast adenocarcinoma, small-cell lung cancer | Tissue-based IFA, immunoblot, western blot |
| PCA-2 (i.e. MAP1B) (Vernino and Lennon; Gadoth *et al.*)[36,37] | Intracellular | Polyradiculoneuropathy, cerebellar ataxia, encephalitis | Small-cell lung cancer | Tissue-based IFA, western blot |
| SOX-1 (AGNA)[a] (Tschernatsch *et al.*; Titulaer *et al.*)[2,21] | Intracellular | Lambert–Eaton myasthenic syndrome, sensory neuronopathy | Small-cell lung cancer | Immunoblot, tissue-based IFA |
| Kelch-like protein 11 (Mandel-Brehm *et al.*; Dubey *et al.*)[3,38] | Intracellular | Rhombencephalitis | Testicular seminoma | Tissue-based IFA, CBA |
| Neurofilament light chain (Basal *et al.*)[39] | | Cerebellar ataxia, encephalopathy | Small-cell lung carcinoma, hepatocellular carcinoma, Merkel cell carcinoma | Tissue-based IFA, CBA |
| PDE10A (Zekeridou *et al.*)[40] | Intracellular | Chorea, dyskinesia, hemiballismus | Renal carcinoma non-small-cell lung cancer, pancreatic cancer | Tissue-based IFA, CBA |
| ANNA-3 (Chan *et al.*)[41] | Intracellular | Cerebellar ataxia, limbic encephalitis | Small-cell lung carcinoma, bronchogenic carcinoma | Tissue-based IFA |
| PCA-Tr (i.e. DNER) (Bernal *et al.*)[42] | Intracellular | Cerebellar ataxia | Hodgkin's lymphoma | Tissue-based IFA, CBA |

[a]a specific biomarker to small-cell lung cancer, rather than a neurological phenotype. AGNA, anti-glial nuclear antibody; ANNA-1, anti-neuronal nuclear antibody type-1; ANNA-2, anti-neuronal nuclear antibody type-2; ANNA-3, anti-neuronal nuclear antibody type-3; CBA, cell based assay; CRMP5, collapsin response-mediator protein-5; DNER, Delta/notch-like epidermal growth factor-related receptor; IFA, immunofluorescence assay; KCTD16, potassium channel tetramerization domain-containing 16; MAP1B, microtubule-associated proteins 1B; PCA-1, purkinje cell antibody type-1; PCA-2, Purkinje cell antibody type-2; PCA-Tr, Purkinje cell antibody type-Tr; PDE10A, phosphodiesterases 10A; SPS, stiff person spectrum.

## Neural-specific antibodies with oncological association

The majority of classic (examples: ANNA-1, CRMP5, PCA-1 etc.) and newly discovered onconeural autoantibodies (examples: KLHL11, PDE10a etc.) with oncological association of ⩾70% target intracellular antigens. Although cell surface antibodies also have potential to be onconeural, this occurs less frequently.

### *Anti-neuronal nuclear antibody type-1 (ANNA-1, i.e. anti-Hu) (intracellular autoantigen)*

ANNA-1 or "anti-Hu" has been described with various paraneoplastic manifestations including sensory neuronopathy, gastroparesis, and limbic encephalitis.[23,24] It has a strong oncologic association (>80% seropositive patients are diagnosed of cancer), particularly small-cell carcinoma in adults and neuroblastoma in children.[24,43,44] ANNA-1 can also occur in cancer patients without the associated PNS.[19,20] The autoantigen (Embryonic Lethal, Abnormal Vision, Drosophila-Like 4 or Hu D antigen) is expressed intracellularly and HuD-specific T cells have been demonstrated to have a pathogenic potential in development of paraneoplastic autoimmunity.[45] Most ANNA-1 IgG-seropositive PNS cases have a refractory course despite aggressive immunotherapy and management of underlying cancer.

### *Purkinje cell antibody type 1 (PCA-1, i.e. anti-Yo) (intracellular autoantigen)*

The most common clinical syndrome associated with PCA-1 IgG is paraneoplastic cerebellar degeneration (PCD).[26] A majority of the reported cases are women, in accordance with this antibody's strong association with gynecological malignancies.[46] However, a few paraneoplastic cases in men with breast or cholangiocarcinoma have also been reported.[47] Among these patients the disease pathogenesis is considered to be mediated by autoantigen-specific cytotoxic T-cell response.[9] CDR2 was initially considered the main Yo/PCA-1 antigen.[48] However, a recent study demonstrated that serum and cerebrospinal fluid (CSF) of patients with PCA-1 IgG-associated paraneoplastic cerebellar degeneration bound to endogenous CDR2 ligand (CDR2L) rather than CDR2.[49] Long-term clinical outcomes in most PCA-1 paraneoplastic cerebellar degeneration cases are relatively poor. Various immunotherapies including corticosteroids, intravenous immune globulins, and plasma exchange for management of this syndrome have been investigated but with limited success.[50,51] Early detection with management of underlying tumor and concomitant immunosuppressive therapy appears to be the most important factors in long-term prognosis of these cases.[52]

### *Collapsin response-mediator protein-5 (CRMP5, i.e. anti-CV2) (intracellular autoantigen)*

CRMP5 IgG has been described in association with paraneoplastic peripheral neuropathy, cranial neuropathy, gastroparesis, encephalitis, cerebellar ataxia, myelopathy, and chorea.[28,53] Certain radiological features such as T2/Fluid-attenuated inversion recovery (FLAIR) hyperintensities involving the striatum have been described among patients presenting with chorea or involuntary movements.[40,53] This is another antibody with a strong cancer association (>80%), especially with small-cell lung cancer or thymoma.[29] Management of underlying malignancy and early initiation of immunotherapy may be associated with a favorable outcome. Outcomes also vary based on the clinical phenotypes. CRMP5 polyradiculoneuropathies appear to be more refractory compared with paraneoplastic myelopathies.

### *Anti-neuronal nuclear antibody type-2 (ANNA-2, i.e. anti-Ri) (intracellular autoantigen)*

ANNA-2 IgG was initially described in association with opsoclonus–myoclonus syndrome and cerebellar ataxia in women with breast cancer.[54] High breast cancer association was also supported by a recent French study.[30] In the men, there was more heterogeneity of cancer types, with lung and bladder cancer most commonly identified. Brainstem syndromes and cerebellar syndromes are the most common neurological presentations.[30,31] Myelopathies, peripheral/cranial neuropathies and encephalitis with or without seizures have also been described.[30] Laryngospasm and/or jaw dystonia has been reported in up to 25% of ANNA-2 paraneoplastic encephalitis patients.[31] Disease severity is highlighted by 60% of patients requiring a wheelchair at nadir. However, a considerable proportion of cases improved with immunosuppressive and tumor-directed therapies.[31,55]

### *Ma2 (intracellular autoantigen)*

Paraneoplastic limbic and/or diencephalic encephalitis is the typical clinical phenotype associated with Ma2 IgG.[8,56] Some of these patients also present with secondary narcolepsy.[57] T2/FLAIR hyperintensities

(with or without associated gadolinium enhancement) involving the medial temporal lobes, diencephalon or brainstem have been described among these cases. Clinical presentations mimicking motor neuron disease have also been described.[17] Anti-Ma2 antibodies are strongly associated with testicular tumors (usually non-seminomatous germ cell tumors) in young men and non-small-cell lung cancer in older patients with co-existing Ma1 IgG.[32,33] A majority of Ma2 IgG-seropositive cases have a refractory course. However, better clinical outcomes have been associated with a male gender, a younger age (<45 years), an absence of anti-Ma1 antibodies, and/or a testicular tumor with complete response to treatment.[32]

### *Amphiphysin (intracellular autoantigen with transient cell surface expression)*

Amphiphysin IgG was initially described in women with paraneoplastic stiff person syndrome and breast cancer.[34,58] Since its initial description, the clinical phenotype has expanded with description of paraneoplastic neuropathies, cerebellar ataxia and limbic encephalitis amphiphysin seropositive cases.[59,60] Common neuropathy phenotypes associated with amphiphysin seropositivity include polyradiculoneuropathy and sensory neuronopathy.[59] Breast cancer and small-cell lung cancers are the two important oncological associations with amphiphysin seropositivity.[61] Despite being an intracellular synaptic vesicular protein, it transiently appears on the cell surface, providing some pathogenic basis for the amphiphysin autoantibodies.[62] Furthermore, animal models with passive transfer of amphiphysin IgG have been demonstrated to develop a clinical phenotype resembling Amphiphysin IgG seropositive patients.[62,63]

### *Purkinje cell antibody type 2 (PCA-2) or microtubule-associated proteins 1B (MAP1B) (intracellular autoantigen)*

PNS associated with this antibody are varied.[36,64] However, one of the most common clinical phenotypes appears to be peripheral neuropathy.[65] A considerable proportion of peripheral neuropathy cases have co-existing central nervous system (CNS) involvement. The most common oncological association among these cases is small-cell lung cancer. Among the subgroup of cases with peripheral neuropathy, MAP1B seropositivity seems to have a more favorable outcome and survival compared with those with ANNA-1 neuropathies.[65]

### *Anti-glial nuclear antibody (AGNA, i.e. SOX1) (intracellular autoantigen)*

SOX1 antibodies have been described in association with PNS and small-cell cancer, especially Lambert–Eaton myasthenic syndrome (LEMS).[66,67] They do not appear to have a strong association with a particular neurological phenotype, but seem to be cancer-specific serological biomarkers.[21,67] In a study of small-cell cancer patients without PNS, 15% of cases were found to be seropositive for SOX1 IgG.[21]

### *Kelch-like protein 11 (KLHL11) (intracellular autoantigen)*

KLHL11 is a novel onconeural antibody associated with rhombencephalitis phenotype (brainstem and/or cerebellar involvement)[3,38] and a few cases of limbic encephalitis with or without rhombencephalitis.[38] In a considerable proportion of cases, hearing loss or tinnitus precedes encephalitis by weeks to months.[5,38] The most common oncological association is testicular germ cell tumors, primarily seminoma. Extra-testicular seminomas in the mediastinum or retroperitoneum have been detected in some patients.[38]

### *Neuronal intermediate filament-light chain (NFl) (intracellular autoantigen)*

NFl IgG has been described among patients with PNS, with encephalopathy and/or ataxia as the predominant neurological manifestations.[39] Sixteen of these 21 cases (77%) were found to have malignancies, commonly neuroendocrine tumors. Reports of clinical outcome following immunotherapies were limited to seven patients, five of whom improved.

### *Phosphodiesterases 10A (PDE10A) (intracellular autoantigen)*

PDE10A IgG was recently described among seven patients with PNS, with movement disorders as the predominant presentation.[40] Six of the seven patients had detectable underlying cancers (lung cancer $n=3$, renal adenocarcinoma $n=2$, pancreatic adenocarcinoma $n=1$).

### *Gamma-aminobutyric acid B-receptor (GABA-B-R) (cell surface autoantigen)*

GABA-B-R encephalitis commonly presents with refractory non-convulsive status epilepticus and/or limbic encephalitis.[68,69] The median patient age is

61 years, and most are men. GABA-B-R antibodies have been associated with malignancy in 50–60% of cases, usually small-cell lung cancer. The presence of co-existing potassium channel tetramerization domain-containing (KCTD)16 antibodies increases the cancer association to 95%.[70]

### *Metabotropic glutamate receptor 5 (mGlur5) (cell surface autoantigen)*

mGlur5 autoantibodies have been described in association with Ophelia syndrome which presents with encephalopathy, mood disturbances, and seizures.[71] Hodgkin's lymphoma is the most common malignancy reported among mGlur5 IgG-seropositive patients, though small-cell lung cancer has also been reported.[72]

### *α-amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid (AMPA-R) (cell surface autoantigen)*

Limbic encephalitis is a common neurological presentation for AMPA-R IgG-seropositive cases, though phenotypic variability ranges from minimal symptoms to fulminant panencephalitis.[73,74] A considerable proportion of these cases (40–60%) have an underlying neoplasm, including small-cell lung cancer, adenocarcinoma of breast, or thymoma.[73,75] (Table 3).

### *N-methyl-D-aspartate-receptor (NMDA-R) (cell surface autoantigen)*

NMDA-R encephalitis can be associated with a neoplasm in 20–40% of cases.[77,85] The majority (94%) of these are ovarian teratomas, though other tumors reported include extra-ovarian teratomas, Hodgkin's lymphoma, small-cell lung cancer, and neuroblastoma.[69,86] Patients are typically young women presenting with a prodrome, subacute neuropsychiatric manifestations, and eventually seizures, encephalopathy, dyskinesias, or autonomic dysfunction.

### *Contactin-associated protein 2 (CASPR2) (cell surface autoantigen)*

CASPR2-IgG is associated with thymomas in about 20% of cases, though other tumors have been reported rarely (melanomas).[11,37] CASPR2-IgG can manifest as Morvan's syndrome, peripheral nerve hyperexcitability, limbic encephalitis, cerebellar dysfunction, painful small-fiber neuropathies associated with neuropathic pain, or epilepsy.[37,87,88]

### *Leucine-rich glioma-inactivated protein 1 (LGI1) (cell surface autoantigen)*

LGI1-IgG is associated with thymoma in about 5–15% of cases; rare cases of squamous cell lung cancer have also been reported.[37,79,80] The frequency of underlying neoplasm (especially thymoma) is higher (40%) among patients who are positive for both LGI1 and CASPR2-IgGs.[37] LGI1-IgG is commonly associated with epilepsy (including faciobrachial dystonic seizures or pilomotor seizures), limbic encephalitis, and/or cognitive decline.[79]

## Cancer screening and surveillance

Computed tomography (CT) of the chest, abdomen, and pelvis with contrast is recommended as initial screening for associated malignancies.[89,90] Scrotal ultrasound should be completed in all males. For screening of breast cancer, mammograms should be considered in all female patients. Transvaginal sonography and/or pelvic magnetic resonance imaging (MRI) are useful in the diagnosis of ovarian teratoma or adenocarcinoma.[91] Managing physicians should perform a careful skin examination with subsequent evaluation for skin lesions concerning for malignant melanoma.

If initial radiological assessment does not detect any malignancy, [$^{18}$F]fluorodeoxyglucose positron emission tomography (FDG-PET) should be performed,[89,90] which has been demonstrated to have a higher sensitivity compared with CT screening alone for occult malignancy.[92–94] Among patients with negative initial radiological studies, FDG-PET improves cancer detection rates by approximately 20%.

A retrospective study of 104 patients suspected of PNS (73 patients were seropositive for neural autoantibodies) demonstrated an increased sensitivity of FDG-PET scan to identify occult tumor. Among 10 patients with pathologically confirmed malignancies, five were picked up only on FDG-PET. Three were detected both on FDG-PET and CT scan.[95] Two patients, with fallopian tube adenocarcinoma and spindle cell uterine carcinoma, had negative FDG-PET.

If no tumor is detected at the time of PNS diagnosis, cancer surveillance should be done every 6 months for 4 years in PNS with onconeural antibodies, except in LEMS, where 2 years is sufficient.[8,96]

**Table 3.** Neural-specific antibodies with moderate to low paraneoplastic associations.

| Antibody | Antigen target location | Common neurological presentations | Cancer association (probability of detecting underlying cancer) | Antibody detection methodology |
|---|---|---|---|---|
| GABA-B-R (Jeffery *et al.*; van Coevorden-Hameete *et al.*; Lancaster *et al.*)[68,70,76] | Cell surface | Limbic encephalitis, status epilepticus | Small-cell lung cancer (40–60%) (co-existing KCTD16 IgG seropositivity increases the cancer association to 95%) | Tissue-based IFA, CBA |
| mGlur5-R (Spatola *et al.*)[72] | Cell surface | Limbic encephalitis | Hodgkin's lymphoma (40–50%), small-cell lung cancer (rare) | Tissue-based IFA, CBA |
| AMPA-R (Hoftberger *et al.*; Joubert *et al.*)[73,74] | Cell surface | Limbic encephalitis | Small-cell lung cancer, adenocarcinoma of breast, thymoma (40–60%) | Tissue-based IFA, CBA |
| NMDA-R (Dalmau *et al.*; Irani *et al.*)[77,78] | Cell surface | Neuropsychiatric dysfunction, oral dyskinesias, seizures, encephalitis | Ovarian teratoma (20–40%) | Tissue-based IFA, CBA |
| CASPR2 (Irani *et al.*; Gadoth *et al.*)[37,79] | Cell surface | Limbic encephalitis, autoimmune epilepsy, peripheral nerve hyperexcitability | Thymoma (<20%), melanoma (rare) | CBA, tissue-based IFA |
| LGI1 (Irani *et al.*; Gadoth *et al.*; Virupakshaiah *et al.*)[37,79,80] | Cell surface | Autoimmune epilepsy/ encephalitis | Thymoma (<20%), squamous cell lung cancer (rare) | CBA, tissue-based IFA |
| GFAP (Dubey *et al.*; Flanagan *et al.*)[81,82] | Intracellular | Meningoencephalomyelitis | Ovarian teratoma (<20%) | Tissue-based IFA, CBA |
| DPPX (Tobin *et al.*)[83] | Cell surface | Encephalopathy, CNS hyperexcitability with myoclonus, GI dysmotility | Lymphoma (<20%) | Tissue-based IFA, CBA |
| mGlur1-R (Lopez-Chiriboga *et al.*)[84] | Cell surface | Cerebellar ataxia | Hodgkin's lymphoma (<20%) | Tissue-based IFA, CBA |

AMPA, α-amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid; CASPR2, contactin-associated protein 2; CBA, cell based assay; CNS, central nervous system; DPPX, dipeptidyl-peptidase-like protein 6; FBDS, faciobrachial dystonic seizures; GABA-B-R, gamma-aminobutyric acid (GABA)-B-receptor; GFAP, Glial Fibrillary Acidic Protein; GI, gastrointestinal; IFA, immunofluorescence assay; LGI1, leucine-rich glioma-inactivated protein 1; mGlur1-R, metabotropic glutamate receptor 1; mGlur5-R, metabotropic glutamate receptor 5; NMDA-R, N-methyl-D-aspartate-receptor.

## Management

There are limited studies evaluating treatment efficacy for PNS.[97] Accordingly, treatment is largely based on expert opinion. Our discussion here will focus on how our practice approaches such cases, with brief mentions of alterative agents that may be used.

The two major principles for PNS management are treatment of the underlying cancer and immunotherapy initiation. This combined oncologic and immunologic therapy should be initiated as soon as possible to minimize irreversible neuronal loss and severe neurological disability.[98]

Immunotherapy response may vary based on timing (symptom onset to treatment duration) and, to some extent, the type of onconeural antibody. PNS disorders with antibodies to intracellular autoantigens and cytotoxic T-cell-mediated pathogenesis may have a more refractory course, such as PCA-1[9] or KLHL11.[3] On the other hand, PNS associated with neural cell surface antibodies (e.g. CASPR2 IgG or LGI1 IgG-associated disorders with

underlying thymoma) have been demonstrated to have a more favorable clinical outcome.[37] Among these cases, neuronal or glial function is impaired by the autoantibodies, but there is absence of cytotoxic T-cell-mediated neuronal destruction early in the disease course.[7]

## Immunotherapy

Acute immunotherapies should be utilized as soon as a PNS diagnosis is suspected, and alternative etiologies, such as infections or metabolic dysfunction, have been reasonably excluded. In our practice, we do not wait for autoantibody results before commencing immunotherapy, especially if the clinical presentation (Table 4) and oncological association are highly suggestive of paraneoplastic disorder, for example subacute sensory neuronopathy in a patient with small-cell lung cancer.[22] As previously discussed, early and aggressive approach among PNS is necessary to minimize long-term disability.

The acute therapies we utilize at our institution in an inpatient or outpatient setting include the following: intravenous methyl prednisone (IVMP), intravenous immunoglobulin (IVIG), and plasma exchange (PLEX). At times these agents can be used in combination such as IVMP and plasmapheresis, rather than waiting to see effect of one first-line agent before initiating another.[100] While following this approach, we also utilize CSF profiles, MRIs or PET brain, as paraclinical biomarkers of ongoing neuroinflammation. In the inpatient setting, we utilize a high-dose IVMP 1 g daily over 3–5 days as the first-line acute immunotherapy for PNS, especially if there is no contraindication. We monitor for clinical response for an additional 2–5 days after completion of the IVMP regimen before utilizing either plasmapheresis (5–7 sessions over 7–14 days) or IVIG (2 g/kg for 5 days).

In the outpatient setting, we gradually increase the interval between IVMP infusions. Based on this concept, we have formulated 6 week and 12 week immunotherapy regimens of IVMP which are commonly used in our institution. This several week trial of immunotherapy allows a longer period to assess response, which may be delayed or be too subtle to detect with only a hyper-acute immunotherapy trial.[101] If the patient has contraindications for IVMP (active infections, poorly controlled diabetes, chronic hepatitis or tuberculosis, etc.), a 6 week or 12 week course of IVIG may be considered.[101] At the end of the trial, patients are re-evaluated in autoimmune neurology clinic (ideally within 1 week of last infusion) to ascertain the treatment response using objective assessment such as neurological examination, brain MRI with gadolinium, PET brain, electrodiagnostic studies, and formal cognitive tests.

Seizures in paraneoplastic encephalitis or pain in paraneoplastic neuropathies may show early improvement within 4–6 weeks of initiating immunotherapy.[28,102] Conversely, cognitive impairment, motor or sensory deficits, usually recover much more slowly.

Although often used for maintenance therapy, second-line agents, such as rituximab and cyclophosphamide, can be utilized early in the disease course, especially among patients meeting definite PNS diagnostic criteria (Table 5).[52] However, in patients who had a delayed diagnosis (symptom onset to diagnosis more than 2 years) or whose neurological presentation are not consistent with classic phenotype, we re-evaluate the patient in our autoimmune neurology clinic after the initial trial of 12 week acute therapy to determine the immunotherapy response before considering further immunotherapy escalation. These decisions can be challenging, and in such scenarios referral to tertiary care neuroimmunology center should be considered.

If we plan to initiate a second-line or long-term therapy after completion of acute immunotherapy, we often utilize a cross-taper. Many of the second-line agents (such as mycophenolate or azathioprine) have a delayed onset of efficacy. In these cases, we usually start the patient on a gradual 12–16 week prednisone taper to avoid relapses while the second-line agent reaches therapeutic efficacy.

For PNS where a cytotoxic T-cell-mediated response is suspected, based on the onconeural antibodies targeting intracellular antigens or histopathology (e.g. nerve biopsy in paraneoplastic polyradicloneuropathy), we prefer utilizing therapies such as cyclophosphamide, mycophenolate mofetil or azathioprine which target all lymphocyte lineages, both B and T cells. The decision between these agents is determined by the severity of disease progression. In more aggressive paraneoplastic presentations either oral or intravenous cyclophosphamide is preferred. Careful monitoring for side effects of long-term immunotherapy is critical. Surveillance includes monitoring of blood

**Table 4.** Common first-line immunotherapies.*

| Drug | Route (dose) | Mechanism of action | Adverse effects | Monitoring |
|---|---|---|---|---|
| Intravenous methyl prednisone (IVMP) | IV (1000 mg for 3–5 days then weekly for 6–12 weeks) | Inhibits NF-KB main pathway in inflammation by release of cytokines required for aggregation of B and T cells. | Hyperglycemia, osteoporosis, avascular necrosis, adrenal failure, immunosuppression predisposing to infections, GI ulcers. | For chronic steroid therapy, we recommend:<br>A) Bone density screening and prophylaxis with supplemental calcium and vitamin D. Bisphosphonates can be considered if appropriate.<br>B) Gastritis prophylaxis with PPI or H2 antagonist.<br>C) *Pneumocystis jiroveci* pneumonia prophylaxis with Trimethoprim/ sulfamethoxazole, dapsone, or pentamidine. |
| Intravenous immunoglobulins (IVIG) | IV (0.4 mg/kg daily for 3–5 days, then weekly for 6–12 weeks) | Binds pathogenic autoantibodies, inhibits complement cascade. | Hypercoagulability, anaphylaxis if there is IgA deficiency, autoimmune hemolytic anemia, renal failure, acute tubular necrosis, pulmonary edema. | Consider checking for IgA deficiency before infusion. Due to the high risk of thrombotic events, use with caution in patients with prior DVT or pulmonary embolism. Due to potential for renal toxicity, monitor for tubular necrosis and renal failure. |
| Plasma exchange (PLEX) | IV | Removes autoantibodies, cytokines, and complement cascades thereby reducing inflammation. | Risk of infections and pneumothorax due to central line placement for the infusions. | Electrolytes, fibrinogen. Primarily used as adjunctive therapy along with other modalities, but can be used as monotherapy as well. |

DVT, deep vein thrombosis; GI, gastrointestinal; H2, histamine-H2 receptor; IV, intravenous; IVIG, intravenous immunoglobulins; IVMP, intravenous methyl prednisone; NF-KB, nuclear factor kappa B; PLEX, plasma exchange; PPI, proton pump inhibitor.
*There are limited studies evaluating treatment efficacy for paraneoplastic neurological syndromes. Treatment is largely based on expert opinion. This discussion focuses on how our practice approaches such cases with brief mentions of alterative agents that may be used.

**Table 5.** Common second-line immunotherapies.*

| Drug | Route (dose) | Mechanism of action | Adverse effects | Monitoring |
|---|---|---|---|---|
| Mycophenolate mofetil | Oral (start at 500 mg twice per day. If tolerated, then increase to 1000 mg twice per day. Typical goal dose: 2000 mg per day). | Inhibits inosine monophosphate dehydrogenase required for synthesis of nucleotides thus inhibiting proliferation of T and B cells. | GI distress, increased predisposition to infections including CMV, skin malignancy, CNS lymphoma, cytopenia. Due to the high risk of neural tube defects in 1st trimester or pregnancy, recommend advising women to avoid pregnancy. | Baseline CBC, creatinine, pregnancy test. After initiation, check CBC weekly for 1 month, then every 2 weeks for 2 months, then monthly for indefinitely. |
| Azathioprine | Oral (start at 1.5 mg/kg/day. If tolerated, increase to 2 mg/kg/day. Further increases in dose depend on the MCV or monitoring results. Typical goal dose: 2–3 mg/kg/day). | Inhibits purine synthesis thus preventing proliferation of T and B cells. | Cytopenias, hypersensitivity reactions, rarely liver damage and pancreatitis. | Baseline CBC, creatinine, LFT, TPMT assay, pregnancy test. After initiation, check CBC and LFT weekly for 1 month, then every 2 weeks for 2 months, then monthly for indefinitely. |
| Methotrexate | Oral (15–25 mg weekly). | Folic acid analog, acts by inhibiting DHFR preventing purine, pyrimidine synthesis thus inhibiting DNA synthesis and cell proliferation. | Cytopenias, hepatotoxicity. | Baseline CBC, creatinine, LFT, pregnancy test. Monitor CBC, creatinine, and LFT every2–4 weeks for 3 months, then every 8–12 weeks for 3 months, then every 3 months while on therapy. |
| Rituximab | IV (Initial loading dose: 1000 mg once, followed by another 1000 mg dose 2 weeks later. Maintenance dosing: 1000 mg every 6 months). | Antibody that binds to CD-20 causing B-cell apoptosis. Also has complement and antibody-mediated cytotoxicity causing depletion of B cells. | Hypersensitivity reactions, fever cytopenias, reactivation of prior viral infections such as hepatitis or PML. | Check baseline pregnancy test, hepatitis-B serology, and tuberculosis serology. Consider checking baseline hepatitis-C serology. During rituximab treatment, can consider checking CD19 lymphocyte subset starting at 5–6 months post infusion if used to guide redosing decisions. |
| Cyclophosphamide | IV (0.6–1.0 g/m$^2$ monthly for 6 months) Oral (Typical dosing: 2mg/kg, dosing based on GFR). | Alkylating agent that causes irreversible DNA cross-linking preventing proliferation of cells. | Hemorrhagic cystitis, nausea/vomiting, cardiotoxicity, secondary malignancy like AML, bladder cancer, cytopenias, alopecia sterility (recommend discussion of sperm/egg banking prior to initiation). Mesna can be used prophylactically to prevent hemorrhagic cystitis. | Check baseline CBC, creatinine, LFT, pregnancy test. During treatment, monitor CBC and urinalysis weekly for 1 month, then every 2 weeks for 2 months, then monthly while on treatment. |

AML, acute myeloid leukemia; CBC, complete blood count; CMV, cytomegalovirus; CNS, central nervous system; DHFR, dihydrofolate reductase; GFR, glomerular filtration rate; GI, gastrointestinal; LFT, liver function tests; TPMT, thiopurine methyltransferase.
*There are limited studies evaluating treatment efficacy for paraneoplastic neurological syndromes. Treatment is largely based on expert opinion. This discussion focuses on how our practice approaches such cases with brief mentions of alterative agents that may be used.

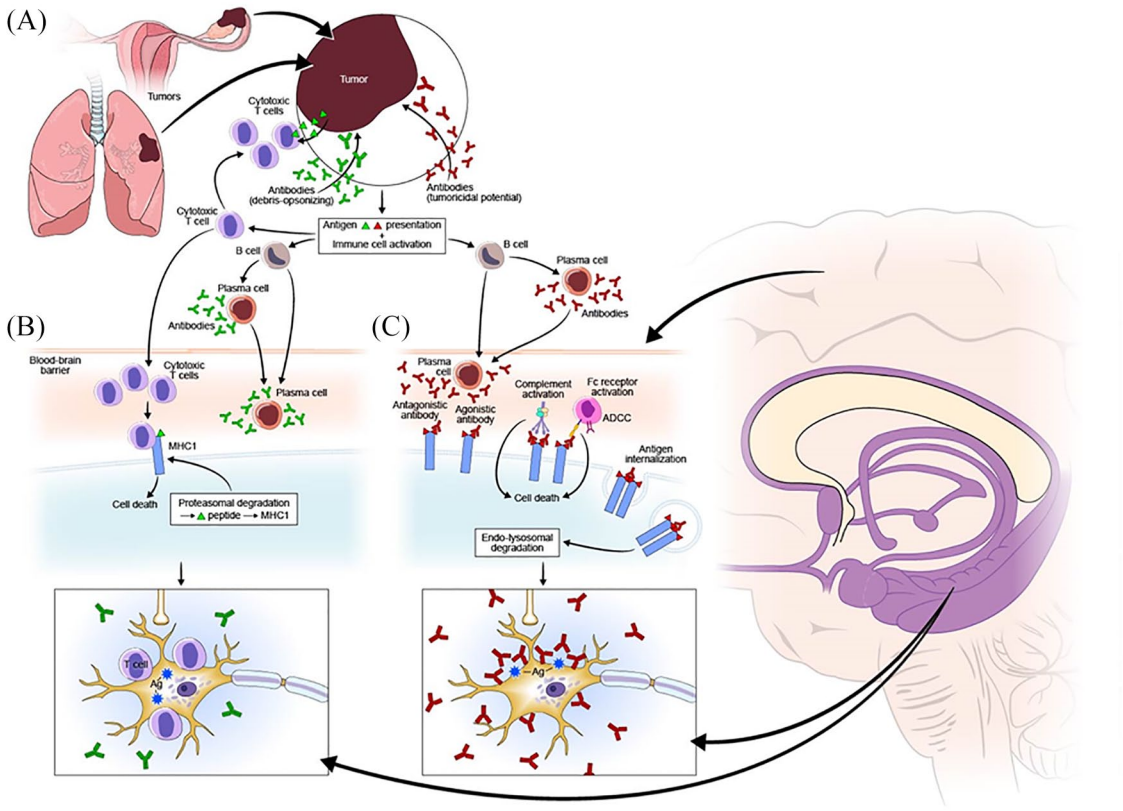


**Figure 1.** Pathophysiological mechanisms for paraneoplastic neurological disorders. Tumor-targeted immune responses are initiated by proteins expressed in the plasma membrane, nucleus, cytoplasm, or nucleolus of certain cancer cells (A). These antigens are also expressed in neurons or glial cells and thus are coincidental targets. Intracellular antigens are not accessible to immune attack *in situ*, but peptides derived from intracellular proteins are displayed on upregulated MHC class I molecules after breakdown in the proteasome and in turn are targeted by peptide-specific cytotoxic T cells (B). Antibodies (e.g. anti-Hu or ANNA-1) targeting these intracellular antigens are not pathogenic but serve as diagnostic markers in clinical practice of a T-cell-predominant immune response. In contrast, antibodies directed at neural cell surface antigens (e.g. N-methyl-D-Aspartate [NMDA] receptors) are effectors through multiple mechanisms (C). (Reprinted by permission from Springer Nature, H. Mitoma, M. Manto (eds.), Neuroimmune Diseases, Contemporary Clinical Neuroscience. Shelly S, Narayan R, Dubey D. Autoimmune Limbic Encephalitis. 4750161436477).

counts, liver function, and renal function. Among patients with an antibody-mediated PNS, for example GABA-B-R IgG-associated encephalitis, we prefer utilizing rituximab as the second-line agent. Rituximab has also been evaluated in an unblinded trial setting for management of PNS associated with antibodies targeting intracellular antigens; however, only three of the nine patients responded favorably.[103]

Other treatment options which have been evaluated for PNS management but not commonly utilized in our clinical practice include tacrolimus, sirolimus, and human chorionic gonadotropin (hCG). A retrospective case series reported 26 PNS patients who were treated with short course of tacrolimus and prednisone therapy.[104] Subjective improvement was noted in some patients with this combination regimen, but lack of a consistent outcome measure and use of other first/second-line immunotherapies in some patients limits the interpretations of the findings. Sirolimus was also evaluated in a prospective open-label trial of 17 ANNA-1 IgG-seropositive PNS patients but only two patients showed any evidence of improvement.[105] In another uncontrolled, unblinded study of 15 ANNA-1 IgG-seropositive patients, intramuscular hCG (12 week course) was associated with modified Rankin score stabilization in four patients and two patients showed improvement, but the duration of follow-up to assess disease neurologic outcome was relatively short.[106]

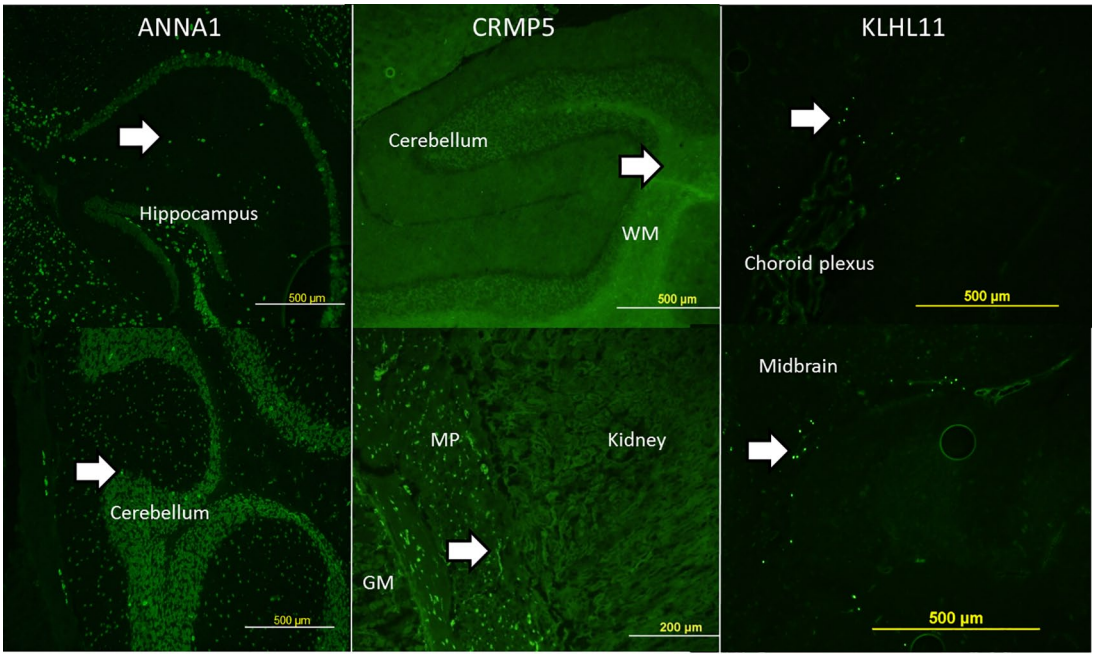


**Figure 2.** Unique indirect immunofluorescence assay on mouse brain with antihuman IgG staining. Key: ANNA-1, anti-neuronal nuclear antibody type-1 (anti-Hu); CRMP5, collapsin response-mediator protein-5; GM, gastric mucosa; KLHL11, Kelch-like Protein 11; MP, myentric plexus; WM, white matter.

We recommend elemental calcium, at least 1500 mg/d and vitamin D 1000 IU/d for all patients taking chronic corticosteroids, as per American Rheumatology Task Force recommendations.[107] Furthermore, baseline and follow-up bone densitometry should be considered in patients requiring more than 3 months of glucocorticoid treatment. If bone densitometry is low, bisphosphonate treatment may be required. We prescribe proton pump inhibitors for patients on chronic glucocorticoid to prevent gastritis or gastric ulceration.[100] We also recommend *Pneumocystis jiroveci* pneumonia prophylaxis in all patients on chronic immunosuppression. Trimethoprim/sulfamethoxazole double-strength tablet three times per week is the commonly utilized prophylactic antibiotic. Alternatives for patients allergic to sulfa drugs or those with significant medication interactions with trimethoprim/sulfamethoxazole are daily oral dapsone or monthly inhaled pentamidine.

As the immune response contributes to limiting cancer growth and metastases, immunosuppression may impact tumor recurrence and outcomes. This has been demonstrated in studies analyzing effect immunosuppression on Merkel cell cancer and cutaneous squamous cell cancer of head and neck.[108,109] In patients with cutaneous squamous cell carcinoma, immunosuppression was associated with worse 5-year disease-specific survival (68% *versus* 84%) and overall survival (37% *versus* 59%).[108] However, a considerable number of these patients had immunosuppression secondary to medical comorbidities, such as lymphoma or leukemia (27%) and HIV (2%), rather than immunosuppressive medications. Additionally, immunosuppression among patients with metastatic Merkel cell carcinoma and anal cancer was also associated with a higher rate of cancer recurrence.[110,111] However, data regarding impact of the immunosuppression on cancer outcome among patients with paraneoplastic are still limited. Patients who are seropositive for onconeural autonantibodies have been demonstrated to have better cancer outcomes compared with seronegative counterparts.[21] Furthermore, in the majority of PNS cases cancer is usually detected at a limited or early stage.[28] Furthermore, immunosuppression may also increase the risk of chemotherapy toxicity.[8] Therefore additional prospective studies may be needed to assess cancer outcome and recurrence among PNS cases who receive chronic immunosuppression.

Despite these concerns, for the majority of PNS cases, the neurological benefit of initiation of

aggressive immunotherapy early in the disease course outweighs the potential risk. In most PNS cases, disability from neurological dysfunction appears to affect the morbidity much more than the underlying cancer. A team-based approach with frequent discussions with oncologists is required, especially for PNS cases with advanced cancers.

## Management of immune checkpoint inhibitor-related neurological adverse events

As the cancer indications of immune checkpoint inhibitors (ICIs) broaden, patients with classic paraneoplastic phenotypes are being encountered,[112] including limbic encephalitis in association with ANNA-1 IgG,[113] LEMS in association with P/Q-type voltage-gated calcium channel antibodies,[114,115] and Ma2 IgG-associated neurological syndromes.[17] These patients with paraneoplastic phenotypes appear to have a clinical course and disease severity similar to their classic paraneoplastic counterparts.[112]

In accordance with current society consensus guidelines[116,117] our current practice is to hold ICI therapies for all grade 3–4 neuro-toxicity.[112] We treat all severe neurological ICI related adverse event (N-irAE) cases with corticosteroids.[118] Cases that respond favorably to corticosteroids are tapered off corticosteroids over 4–6 weeks. Patients who remain refractory to corticosteroid therapy 7–10 days after initiation of treatment receive escalated therapy with plasmapheresis, IVIG, corticosteroid-sparing immunosuppressive agents.[117,119,120]

Retreatment of these patients with ICIs is always a difficult decision due to the increased risk of N-irAE relapse.[118] If ICIs are to be reinitiated, we reduce the risk of N-irAE relapse by treating the patient with corticosteroids to the point of symptom resolution or stabilization. Then we recommend observing the patient for a period of 2–8 weeks, prior to reinitiating ICIs.

## Conclusion

With a growing list of serological biomarkers and increased use of ICIs, we are diagnosing more and more patients with paraneoplastic neurological disorders. Early treatment of underlying cancer and aggressive immunotherapy, the two basic principles of the management of these disorders, has not changed significantly since its initial description. However, over the last three decades we have been able to collect a significant amount of clinical data, treatment data, and long-term follow-up data for these disorders. It is likely that our approach to managing these cases will continue to evolve as immunosuppressive therapies are investigated in prospective open-label or randomized control trials.

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