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Diagnosis and Management of Paraneoplastic Neurologic Disorders

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Opinion Statement

Paraneoplastic neurologic disorders (PND) are a heterogeneous group of immune-mediated neurological disorders associated with systemic cancers. When a PND is diagnosed prompt identification and treatment of the associated tumor is important as PND stabilization and in some cases improvement have been reported after tumor treatment. The cancer however, may be small and difficult to detect or the onset of the PND may precede the development of the cancer by months or years. In the latter cases patients often initially present to neurologists or internists who will need assistance from their oncology colleagues to uncover the cancer. It is therefore important to be aware of the associations of common cancers with specific PND syndromes and the significance in some PND of the presence in serum and/or cerebrospinal fluid (CSF) of specific anti-neuronal antibodies. Together, this information can focus the search for the tumor or support continued vigilance. Previously thought to be poorly responsive to therapies, it is now recognized that there is a subgroup of PND, mostly associated with antibodies to antigens on the neuronal cell surface that are highly treatment responsive. Treatments aimed at the PND are mostly immunosuppressive and include corticosteroids, plasma exchange and intravenous immunoglobulins (IVIg). Immunosuppressive chemotherapeutics and B-cell targeting drugs such as rituximab may also be useful. While cancer patients tolerate these therapies there is the risk of increased toxicity when combined with tumor-directed treatments and treatment plans should be coordinated between specialists.

Keywords

paraneoplastic; neurologic; disorder; anti-neuronal; antibody; autoimmune; immune-mediated; immunosuppression; plasma exchange; intravenous immunoglobulins

Introduction

The paraneoplastic neurologic disorders are a varied group of cancer-related neurologic disorders that are known or suspected to be immune-mediated. The tumors most commonly associated with PND are those that express neuroendocrine proteins such as small-cell lung

Conflict of Interest

Myrna R. Rosenfeld and Josep Dalmau declare that they have no conflict of interest.

Human and Animal Rights and Informed Consent

This article does not contain any studies with human or animal subjects performed by any of the authors.

cancer (SCLC), tumors that contain nervous tissue such as teratomas, and tumors that affect organs with immunoregulatory functions such as thymoma. Less common but often associated with highly typical neurologic syndromes are neoplasms of the ovary, breast, and germ-cell tumors of the testis. A variety of paraneoplastic neuropathies are found in association with leukemias, lymphoma, plasma cell dyscrasias and related disorders. These diverse neuropathic syndromes will not be further discussed and are reviewed elsewhere [1•, 2•].

For a patient without a cancer diagnosis, the identification of PND is straightforward if they develop a neurologic syndrome typically associated with cancer (Table 1). It is generally recommended that any patient who develops one of these ‘classic’ PND syndromes undergo cancer screening initially focused on the most commonly associated cancers. The presence of a specific anti-neuronal antibody in serum or CSF will confirm a paraneoplastic etiology. If no cancer is found a more extensive evaluation should be done as rare cancer-antibody associations do occur. In almost 90% of patients with PNDs associated with solid tumors the underlying cancer will be uncovered either at PND presentation or within the first year. Patients in whom PND is strongly suspected but no cancer is identified should undergo periodic cancer screening for at least five years.

In patients with a cancer diagnosis the suspicion that new neurologic symptoms are paraneoplastic in origin is based on whether the neurologic syndrome is typically associated with the patients’ cancer type or anti-neuronal antibody, if present, and the absence of other etiologies including side effects of cancer treatment. Patients in cancer remission who develop typical PND syndromes should be examined for tumor recurrence. General guidelines for cancer screening in patients with PND have been proposed and can help direct the evaluation [3].

The diagnosis of PND is more difficult in patients whose neurologic syndromes may be paraneoplastic but more commonly occur without a cancer association (Table 2). Some of these patients have anti-neuronal antibodies that associate with the neurologic syndrome but occur in patients both with and without cancer and thus are not specific for PND (Table 2) [4•]. The need for an oncologic evaluation is based on the syndrome, clinical suspicion for a cancer, and if present the antibody. For example most patients with myasthenia gravis have anti-acetylcholine receptor antibodies but only 15% of cases are paraneoplastic. However, due to the strong association with thymoma it is recommended that all newly diagnosed patients undergo screening for this specific tumor. In contrast, the Guillain-Barré syndrome may be a paraneoplastic manifestation of Hodgkins’ lymphoma and less commonly a systemic cancer. The lack of specificity for any one cancer type and the relatively infrequent occurrence of Guillain-Barré as a PND argues against routine cancer screening unless there is clinical or laboratory evidence that suggests an underlying cancer [5]. In some cases the co-occurrence of a neurologic syndrome and cancer may simply be coincidental. A paraneoplastic relationship is suggested but not proven by evidence of nervous system inflammation, an atypical presentation or course of the neurologic disease, or response to immunotherapies.

For most PND, neuroimaging with magnetic resonance imaging (MRI) is more important to rule out other causes of neurologic dysfunction such as compression by metastatic lesions or to detect leptomeningeal metastases rather than for making the diagnosis of PND as in many PND neuroimaging will be normal. The main exception is in limbic encephalitis in which abnormalities may be demonstrated using T2 and fluid-attenuated inversion recovery (FLAIR) sequences that likely represent the on-going inflammatory process in the nervous system [6, 7]. The radiologist should be made aware of the possible limbic encephalitis diagnosis so that special attention is given to these sequences. Brain [F18]

fluorodeoxyglucose-positron emission tomography (FDG-PET) in the early stages of some PND of the central nervous system may show hypermetabolism in some regions even when MRI is normal and is likely indicative of the early stages of the inflammatory process [8, 9, 10]. Cerebellar atrophy may be seen at the end stages of cerebellar degeneration.

Anti-neuronal Antibodies

The specificity of some anti-neuronal antibodies for certain PND or some types of cancer helps diagnose the PND and focus the oncologic evaluation (Table 1). The presence of any of these antibodies (including anti-Hu, Yo, CV2/CRMP5, Ri, Ma2, Tr and amphiphysin) is almost invariably associated with cancer and if a cancer is not discovered, the presence of an occult neoplasm must be assumed. However, all PND can occur in the absence of antibodies and antibodies are detectable at low titers in the serum of some patient with cancer without PND [11]. However, the finding of high titers of antibodies in serum or of any titer of antibodies in the CSF is strongly supportive of PND. For those PND that affect the central nervous system, antibody titers in CSF will be higher than in serum or the serum may be negative for antibodies so it is recommended that CSF be studied in all suspected cases.

TREATMENT

For treatment purposes the immune-mediated PND can be divided into those in which the antibodies are pathogenic and those in which cytotoxic T-cells are the main effectors of the neurologic dysfunction. When antibodies are pathogenic the target antigens are mostly neuronal cell surface or synaptic proteins whose function is disrupted by the antibody [12–14]. In these disorders antibody removal often results in neurologic improvement. However antibody-depleting strategies are much more effective when the target antigens are in the periphery (e.g, myasthenia gravis or Lambert-Eaton myasthenic syndrome) as plasma exchange and IVIg are not very effective at decreasing intrathecal antibody titers. For those antibody-mediated disorders of the central nervous system (e.g, anti-NMDA receptor encephalitis), additional immunotherapies are often required [15•].

For those PND that are likely T-cell mediated (e.g, anti-Hu associated encephalomyelitis), immunosuppression or immunomodulation is recommended but responses are less likely as irreversible neuronal damage appears to occur rapidly and early [16]. For these PND data demonstrates a better chance for improvement or stabilization of the PND if immunotherapies are started when the neurologic deficits are not fully established [17, 18]. Exceptions include limbic encephalitis in young men with testicular tumors and anti-Ma2 antibodies and stiff-person syndrome associated with anti-amphiphysin antibodies [19].

Treatment of the Tumor

For all PND, prompt identification and treatment of the tumor is important as this has been found in several series to be the main factor associated with stabilization or improvement of the PND [18, 20]. Patients should be approached and treated as those without PND. Although surgeons are reluctant to take critically ill patients for tumor resection, patients with PND should be quickly and aggressively treated. As an example, patients in intensive care units with anti-NMDA receptor encephalitis tolerate tumor resection and immunotherapies and data shows that these procedures shorten time to recovery and increase the likelihood of full recovery [15•].

Treatment of the PND

Treatments directed at the PND are primarily immunosuppressive and immunomodulatory. Initial therapies often include corticosteroids, plasma exchange, IVIg and/or rituximab.

More aggressive second-line immunosuppression with cyclophosphamide, tacrolimus, or cyclosporine among others, may be used when there is no response to initial treatments and the patient is still losing neurological functions. There are few studies proving efficacy, although several retrospective and small prospective studies support benefit of immunosuppression for some patients and syndromes [15•, 18, 21, 22]. Concerns that the use of immunosuppression in cancer patients will favor tumor growth are not supported by available studies however the simultaneous use of some immunosuppressants and oncologic treatments may result in increased toxicity requiring coordination of care between subspecialties.

Pharmacological Therapies

There are few trials examining optimal treatment strategies for PND. Most treatments are empirically based on data from other autoimmune diseases and reports from cases series and cohort studies. Thus there are no standard dosing regimens specific to PND.

Corticosteroids

Corticosteroids are commonly and empirically used in conjunction with other treatments such as IVIg or plasma exchange.

Dosing: Methylprednisolone 1000 mg/day I.V. for 3 to 5 days is often used initially or in repeating monthly courses. Prednisone 1 mg/kg P.O. daily or 60–80 mg daily may be used as maintenance therapy followed by slow tapering.

Contraindications: Patients with diabetes, underlying infections, hypertension or peptic ulcer disease need to be monitored closely.

Main drug interactions: None.

Main side effects: hyperglycemia, hypertension, leukocytosis, thrombocytosis, peptic ulceration, insomnia, osteoporosis.

Cost/cost effectiveness: Relatively inexpensive.

Cyclophosphamide

Cyclophosphamide is a broad immunosuppressive agent that decreases both humoral and cellular immunity.

Dosing: Varying dosing regimens have been reported in small series. These include 750 mg/m² (body surface area) infused over 1 hour once every 4 weeks; fixed dose of 500 mg per day for 2–4 days per month, or a fixed monthly dose of 1000 mg. All regimens were given I.V.

Contraindications: Patients with diabetes, underlying infections, hypertension or peptic ulcer disease need to be monitored closely. Not to be used during pregnancy.

Main drug interactions: Allopurinol.

Main side effects: Nausea, vomiting, myelosuppression, headache, dizziness, hemorrhagic cystitis.

Special points: Increased risk of myelo- or lymphoproliferative malignancies. The above noted doses do not require Mesna to prevent hemorrhagic cystitis.

Cost/cost effectiveness: Cyclophosphamide is relatively inexpensive however costs are increased due to the need for intravenous hydration and laboratory monitoring.

Intravenous Immunoglobulin (IVIg)

Despite use over many years, the mechanisms by which IVIg modulates immune function are not well understood but it appears to decrease T-cell proliferation, suppress B-cell differentiation and decrease levels of pro-inflammatory cytokines [23]. Thus it has broad range of action and has been used in almost all PND.

Dosing: There is no standard dose. Some patients have received 0.4 gm/kg per day for 3 to 5 consecutive days each month (total dose no more than 2 gm/kg) while others have used 2 gm/kg per month (divided into 2 consecutive daily doses of 1 gm/kg) for three months.

Contraindications: IgA deficiency, previous hypersensitivity, hyperviscosity syndrome, vascular disease, renal insufficiency.

Main drug interactions: None.

Main side effects: Headache, nausea, fever, aseptic meningitis.

Special points: The use of 60 mg I.V. methylprednisolone may decrease the severity of headache

Cost/cost effectiveness: Very expensive.

Rituximab

Rituximab is mostly reserved for those disorders in which antibodies are pathogenic (e.g, anti-NMDA receptor encephalitis) as antibody depleting strategies such as plasma exchange and IVIg are far more effective in depleting peripheral but not central nervous system antibody titers [22]. Furthermore, the depletion of intrathecal B-cells produced by rituximab is durable and can last for 8 or more months [24, 25].

Dosing: Most practitioners use the same dosing as that in patients with lymphoma: 375 mg/m² every week for 4 weeks.

Contraindications: Allergy to mouse proteins and patients with cardiac disease.

Main drug interactions: Use of live virus vaccines.

Main side effects: Hypersensitivity with first infusion including fever, chills, headache and hypotension.

Special points: Infusion reactions can be mitigated by pretreatment with intravenous corticosteroids, anti-histaminics and acetaminophen.

Cost/cost effectiveness: Expensive.

Mycophenolate mofetil

Mycophenolate has been used for long-term immunosuppression and may be useful in disorders such as anti-NMDA receptor encephalitis in which relapses can occur.

Dosing: 1000 to 1500 mg/day P.O. twice a day.

Contraindications: Pregnancy, severe gastrointestinal or renal disease.

Main drug interactions: Live virus vaccines. Macrolide antibiotics decrease mycophenolate blood levels while acyclovir and related drugs may increase levels.

Main side effects: Gastrointestinal symptoms can be severe and myelosuppression.

Special points: Patients require periodic blood cell count monitoring and levels of liver and renal enzymes.

Cost/cost effectiveness: Very expensive.

Interventional Procedures

Plasma Exchange

Plasma exchange reduces serum levels of antibodies and is therefore useful for those PND of the peripheral nervous system directly mediated by antibodies. Plasma exchange also reduces circulating levels of cytokines and other mediators of inflammation that likely contribute to its effectiveness as an immunomodulatory therapy. Plasma exchange tends not to be useful for antibody-mediated PND of the central nervous system likely due to its inability to decrease intrathecal antibody titers.

Procedure: Often performed every other day for a total of 5–6 exchanges. The exact number of exchanges should be adjusted for each patient. Some patients will require maintenance therapy on a monthly or less frequent basis.

Contraindications: Poor medical condition, cardiac insufficiency, coagulopathy.

Complications: Hypotension, cardiac arrhythmias, clotting abnormalities, electrolyte disturbances, muscle cramping, and infection at catheter site.

Special points: Must be performed in hospital setting, usually requires indwelling catheter

Cost/cost effectiveness: Expensive. For some disorders patients may have dramatic responses, and thus the cost of the procedure outweighs the cost of long-term medical care for the untreated patient.

Protein A column immunoabsorption

Although the exact mechanism of action of protein A immunoabsorption is not well understood, data suggests it results in a reduction of circulating IgG antibodies and immune complexes, and an increase in natural killer cell activity.

Procedure: There is no set standard procedure. In one reported clinical trial patients were treated with protein A immunoabsorption therapy twice a week for 3 weeks for a total of 6 sessions [26]. At each session approximately 250–300 milliliters of plasma were perfused over the column.

Symptomatic and supportive therapy

Patients with brainstem or cerebellar dysfunction may require wheelchairs and feeding tube placement. Seizures associated with encephalitis often respond to conventional anti-epileptics. Neuropathic pain and sensory dysesthesias in patients with neuropathies may be treated with antidepressants including the tricyclics (e.g., amitriptyline) and the selective serotonin reuptake inhibitors, duloxetine and venlafaxine. The anti-epileptic drugs gabapentin and pregabalin may also be useful in some patients. For severe pain tramadol and opioids are available.

Pediatric Considerations

The most commonly encountered paraneoplastic syndrome in children is opsoclonus-myoclonus occurring in children with neuroblastoma [27]. Treatment of the tumor and corticosteroids, adrenocorticotrophic hormone, plasma exchange, IVIg, or rituximab, result in improvement in one half to two thirds of patients although many children have residual cognitive and behavioral deficits [28]. Anti-NMDA receptor encephalitis is increasingly recognized in the pediatric population and as in adults is often responsive to

immunotherapy. Tumors (usually teratoma) may occur in children but the disorder is more often not paraneoplastic in this population [29].

Other Procedures: Anti-neuronal Antibody Testing

Any PND may occur without associated antibodies, and anti-neuronal antibodies are occasionally found at low titers in patients with cancer without neurologic symptoms [30]. If an antibody is found, but is one not usually associated with the patients' neurologic syndrome, other causes for the neurologic dysfunction should be considered. Similarly, if the detected cancer is not the histologic type typically found in association with the antibody a second neoplasm should be suspected. When PND affect the brain, spinal cord or dorsal root ganglia, antibody titers will be higher in the CSF than serum. Therefore, if serum tests negative and there is suspicion of PND, CSF must be studied. This may also provide other supporting evidence of PND such as the presence of inflammatory cells.

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Table 1

Classic Paraneoplastic Neurologic Syndromes, Cancer and Antibody Associations and Responses to Therapy

Patients who develop one of these syndromes should undergo cancer screening				
Syndrome	Common Cancer Associations	Anti-neuronal Antibody	Response to Immunotherapy*	Comment
Encephalomyelitis	SCLC	Anti-Hu	Poor	~25% of patients also develop autonomic dysfunction including cardiac dysrhythmias and respiratory failure [31,32]
Encephalomyelitis, uveitis, peripheral neuropathy [33]	SCLC, thymoma	Anti-CV2/CRMP5	Poor	
Subacute sensory neuropathy [31]	SCLC, others	Anti-Hu almost always present with SCLC but not other solid tumors	Poor	May develop alone or in association with encephalomyelitis. ~80% of cases develop before the cancer diagnosis.
Limbic, brainstem, hypothalamic encephalitis	Testicular germ- cell tumors	Anti-Ma2	Responses occur in ~one-third of cases	In young adults: Associated with seminomas and germ- cell tumors of the testis that may be microscopic [34]. In patients over 50 years: lung cancer.
Cerebellar degeneration	Gynecologic, breast	Anti-Yo	Poor	
Cerebellar degeneration, opsoclonus	Gynecologic, breast	Anti-Ri	Poor	Patients can develop laryngospasm and trismus that may respond to botulinum toxin [35].
Cerebellar degeneration	Hodgkins lymphoma	Anti-Tr [36,37]	Responses occur in 20%	
Stiff-man syndrome, encephalomyelitis	Breast, SCLC	Anti- amphiphysin	Reports of some responses; symptomatic treatment for spasms	When not cancer-associated patients often have antibodies to GAD[38]
Opsoclonus- myoclonus	Neuroblastoma in children; Various solid tumors adults	Multiple immune responses have been identified supporting an immune- pathogenesis [39,40]; anti-Ri are found in a subset of women with breast or gynecologic cancers	Yes	Despite responses children may be left with residual cognitive and behavioral deficits [28]. Adults whose tumors are not treated may develop a progressive severe encephalopathy resulting in death [41]
Retinopathy	SCLC	Anti-Recoverin	Rare	Case reports of responses to immunosuppression [42•]

Patients who develop one of these syndromes should undergo cancer screening				
Syndrome	Common Cancer Associations	Anti-neuronal Antibody	Response to Immunotherapy*	Comment
Retinopathy	Melanoma	Anti-retinal bipolar cell	Rare	Case reports of responses to immunosuppression [43]

* : In addition to treatment directed to the tumor; SCLC: Small-cell lung cancer; CRMP: Collapsin response-mediator protein; GAD: Glutamic acid decarboxylase

Table 2

Neurologic Syndromes and Anti-neuronal Antibodies that May or May Not be Cancer Associated

The need for an oncologic evaluation is based on level of suspicion for a cancer, the syndrome and antibody if present.				
Syndrome	Common Cancer Associations	Anti-neuronal Antibody	Response to Immunotherapy*	Comment
Lambert-Eaton myasthenic syndrome +/- cerebellar degeneration	SCLC	Anti-VGCC	Most patients improve [44•]	Paraneoplastic in ~60% of cases.
Myasthenia gravis	Thymoma	Anti-AChR (muscle)	Many patients improve [44•]	Paraneoplastic in ~10% of cases
Autonomic neuropathy	SCLC	Anti-AChR (neuronal) [45]	Case reports suggest isolated responses	Often is not paraneoplastic
Neuromyotonia +/- encephalitis	Thymoma, lung	Anti-CASPR2 [46]	May respond	Paraneoplastic in ~25% of cases. The co-occurrence of neuromyotonia and encephalitis is known as Morvan's syndrome
Anti-NMDA receptor encephalitis[15•]	Teratoma	Anti-NMDA receptor	Often responsive although recovery may be prolonged.	Paraneoplastic in 50% of women > 18 years and < 10% women < 14 years, rare tumor associations in young children and men
Limbic encephalitis	SCLC, thymoma, breast	Anti-AMPA receptor [13]	Yes with a tendency for relapses to occur	Often with prominent psychiatric features; 70% of cases are paraneoplastic.
Limbic encephalitis	Thymoma	Anti-LGI1 [47]	Yes	Associated with short tonic seizures. <10% of cases are paraneoplastic
Limbic encephalitis	SCLC	Anti-GABA(B) receptor [48]	Yes	The most common cause of paraneoplastic limbic encephalitis in SCLC patients after anti-Hu encephalitis. Seizures are prominent; 50% of cases are paraneoplastic
Cerebellar degeneration	Hodgkins lymphoma	mGluR1 [49]	Too few cases reported	
Limbic encephalitis	Hodgkins lymphoma	mGluR5 [50]	Yes	Co-occurrence of limbic encephalitis and Hodgkins

The need for an oncologic evaluation is based on level of suspicion for a cancer, the syndrome and antibody if present.				
Syndrome	Common Cancer Associations	Anti-neuronal Antibody	Response to Immunotherapy*	Comment
				lymphoma is known as Ophelia syndrome
Dermatomyositis	Solid tumors	No specific antibody has been identified	Isolated cases reports of responses	<30% of cases are paraneoplastic [51]

* : In addition to treatment directed to the tumor; SCLC: Small-cell lung cancer; VGCC: Voltage-gated calcium channel; AChR: Acetylcholine receptor;

Caspr2: Contactin-associated protein 2; NMDAR: N-methyl D-aspartate receptor; AMPAR: -amino-3-hydroxy-5-methylisoxazole-4-propionic acid receptor;

LGI1: Leucine-rich glioma inactivated 1; GABA(B): Gamma-amino-butyric acid type B; mGluR1: Metabotropic glutamate receptor-5; mGluR5: Metabotropic glutamate receptor-5