Overview of paraneoplastic syndromes of the nervous system

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INTRODUCTION

Paraneoplastic neurologic syndromes are a heterogeneous group of neurologic disorders caused by mechanisms other than metastases, metabolic and nutritional deficits, infections, coagulopathy, or side effects of cancer treatment. These syndromes may affect any part of the nervous system, from cerebral cortex to neuromuscular junction and muscle (table 1), either damaging one area or multiple areas.

This topic provides an overview of the pathogenesis, diagnosis, and treatment of paraneoplastic neurologic disorders. Individual syndromes are discussed separately.

- (See "Paraneoplastic and autoimmune encephalitis".)
- (See "Paraneoplastic cerebellar degeneration".)
- (See "Paraneoplastic visual syndromes".)
- (See "Opsoclonus-myoclonus syndrome".)
- (See "Paraneoplastic syndromes affecting spinal cord, peripheral nerve, and muscle".)

PATHOGENESIS

The pathogenesis of paraneoplastic neurologic syndromes is incompletely understood, but an immunologic basis is likely for many of them.

Immunologic mechanisms — Immunologic factors are believed to be important because, for many of the disorders, antibody and T cell responses against nervous system antigens have been described. In such cases, the immunologic response is directed against shared antigens that are ectopically expressed by the tumor but otherwise exclusively expressed by

the nervous system (picture 1) [1,2]. Some immunologic targets reside in the testes, which normally express antigens shared with the nervous system [3].

For unknown reasons, the immune system identifies these antigens as foreign and mounts an immune attack against them. Some evidence suggests that normal self-antigens are processed differently in cancer cells than in normal cells, based on the observation that the immune system can mount a T cell response to a normal protein when it is expressed in a cancer cell [4].

Types of antibodies — Antineuronal antibodies may be present in serum and/or cerebrospinal fluid (CSF) of patients with paraneoplastic neurologic syndromes. Some of these antibodies are highly specific for the presence of a cancer, and their detection serves as a marker of paraneoplasia. Other antibodies associate with specific neurologic syndromes that occur with or without cancer; these serve as markers for the neurologic syndrome without distinguishing between a paraneoplastic or nonparaneoplastic etiology.

Antibodies that occur in paraneoplastic disorders can be divided in two categories depending on the location of the antigen:

- **Intracellular antigen** – Antibodies directed against intracellular neuronal proteins are referred to as classical paraneoplastic or onconeuronal antibodies. The detection of these antibodies (table 2) almost always indicates the presence of an underlying tumor. These antibodies are surrogate markers of the paraneoplastic disorder, but in most of these disorders, the pathogenic mechanism is believed to be mediated by cytotoxic T cells.

  Examples include Hu (also known as type 1 antineuronal nuclear antibody [ANNA-1]), Ri (also known as type 2 antineuronal nuclear antibody [ANNA-2]), Yo (also known as Purkinje cell cytoplasmic antibody type 1 [PCA-1]), amphiphysin, Ma2, Tr (also known as delta/notch-like epidermal growth factor-related receptor [DNER]), collapsin-responsive mediator protein 5 (CRMP5), and recoverin.

- **Cell surface or synaptic antigen** – Antibodies directed against neuronal cell surface or synaptic proteins may occur with or without a cancer or tumor association [5]. The frequency of a tumor association varies according to the antibody. These antibodies appear to have direct pathogenic effects on the target antigens [5]. An underlying genetic predisposition may also play a role for some of these disorders [6].

  Examples include antibodies against the N-methyl-D-aspartate (NMDA) receptor, the alpha-amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid (AMPA) receptor, the gamma-aminobutyric acid type A (GABA-A) and type B (GABA-B) receptors, and contactin-associated protein-like 2 (Caspr2), among others (table 2).

Pathogenic effects of antibodies — For most of the classical paraneoplastic antibodies, a pathogenic role has not been proven. However, their presence indicates the paraneoplastic nature of a neurologic disorder and, in many cases, can narrow the search for an occult tumor to a few organs (table 2).

Pathogenic effects have been demonstrated for the following antibodies:

- P/Q type voltage-gated calcium channel antibodies in the Lambert-Eaton myasthenic syndrome (LEMS) [7]
- Acetylcholine receptor antibodies in myasthenia gravis (MG) [8]
- NMDA receptor antibodies in anti-NMDA receptor encephalitis [9-11]
- AMPA receptor antibodies in a subgroup of limbic encephalitis [12,13]
- Ganglionic acetylcholine receptor antibodies in autonomic neuropathy [14]
- Recoverin antibodies in carcinoma-associated retinopathy [15]
- GABA-A receptor antibodies in encephalopathy with refractory seizures [16]
- Leucine-rich glioma inactivated 1 (LGI1) antibodies in a subgroup of limbic encephalitis [17,18]
- Caspr2 antibodies in patients with encephalitis and Morvan syndrome [19]
- Dipeptidyl-peptidase-like protein-6 (DPPX) antibodies in a syndrome of central nervous system hyperexcitability, often associated with hyperekplexia [20-23]
- Metabotropic glutamate receptor 5 (mGluR5) antibodies in encephalitis not restricted to limbic encephalitis [24]

Autoantibodies may also play an important pathogenic role in other syndromes such as the paraneoplastic form of stiff-person syndrome (often associated with amphiphysin antibodies) [25]. (See "Stiff-person syndrome".)

Previously, it had been suggested that some paraneoplastic neurologic syndromes without an identifiable tumor were a result of immune-mediated eradication of tumor cells [26]. In addition, some reports suggested a more limited disease distribution and better outcome among patients with small cell lung cancer (SCLC) who developed immunity to paraneoplastic antigens [27-29]. However, review of large series of patients demonstrates that the oncologic outcome of patients with antibody-associated paraneoplastic syndromes does not significantly differ from that of patients who do not have the antibodies or a paraneoplastic syndrome [30-35].

Nonimmunologic mechanisms — There are also nonimmunologic mechanisms that can be involved in paraneoplastic neurologic syndromes. These include [36]:

- Metabolic abnormalities due to tumoral secretion of hormones or cytokines (eg, hyponatremia due to antidiuretic hormone, hypercalcemia due to parathyroid hormone-related protein, or hypoglycemia due to insulin-like growth factor 2). (See "Hypercalcemia of malignancy: Mechanisms" and "Hypoglycemia in adults without diabetes mellitus: Diagnostic approach".)

- Competition between the tumor and the nervous system for a substrate (eg, carcinoid tumors and tryptophan). (See "Clinical features of carcinoid syndrome".)

- The synthesis by the tumor of immunoglobulins that react with the peripheral nervous system (eg, a distal, symmetric, and slowly progressive sensorimotor peripheral neuropathy in Waldenström macroglobulinemia) and antibodies against myelin-associated glycoprotein (MAG). (See "Epidemiology, pathogenesis, clinical manifestations, and diagnosis of Waldenström macroglobulinemia".)

EPIDEMIOLOGY

Paraneoplastic disorders have an incidence that varies with the neurologic syndrome and type of tumor. The more common syndromes are Lambert-Eaton myasthenic syndrome (LEMS), which affects approximately 3 percent of patients with small cell lung cancer (SCLC), and myasthenia gravis (MG), which affects 15 percent of all patients with thymoma. One or more paraneoplastic neurologic disorders are present in up to 9 percent of patients with SCLC (mostly LEMS, sensory neuronopathy, and limbic encephalitis) [37]; for most other solid tumors, the incidence is far less than 1 percent [38].

Paraneoplastic peripheral neuropathies affect 5 to 15 percent of patients with a paraproteinemia-related disease including multiple myeloma, POEMS (polyneuropathy, organomegaly, endocrinopathy, monoclonal protein, and skin changes) syndrome, multicentric Castleman disease, or lymphoplasmacytic lymphoma/Waldenström macroglobulinemia. Each of these paraproteinemias is associated with different neuropathic syndromes. (See "Paraneoplastic syndromes affecting spinal cord, peripheral nerve, and muscle", section on 'Peripheral nerve' and "Multiple myeloma: Clinical features, laboratory manifestations, and diagnosis", section on 'Neurologic disease' and "Epidemiology, pathogenesis, clinical manifestations, and diagnosis of Waldenström macroglobulinemia" and "POEMS syndrome" and "HHV-8/KSHV-associated multicentric Castleman disease".)

CLINICAL SYNDROMES

Paraneoplastic syndromes may affect any part of the nervous system, from cerebral cortex to neuromuscular junction and muscle (table 1). Some syndromes affect a single area, such as the anterior horn cell in motor neuronopathy. Others affect multiple areas, as in the case of encephalomyelitis.

Central nervous system — Paraneoplastic syndromes of the central nervous system result in dysfunction of the brain and/or spinal cord. Symptoms vary depending on the areas involved. Syndromes are generally named according to the most prominent clinical signs and symptoms.

- **Limbic encephalitis** – Limbic encephalitis is characterized by acute or subacute mood and behavioral changes, short-term memory problems, focal seizures with impaired awareness, and cognitive dysfunction (table 3). Hypothalamic dysfunction may also occur. (See "Paraneoplastic and autoimmune encephalitis", section on 'Limbic encephalitis'.)

  Both paraneoplastic and nonparaneoplastic presentations of limbic encephalitis can occur, and they can be clinically indistinguishable [39]. Onconeuronal antibodies such as anti-Hu and anti-Ma2, when present, almost always associate with an underlying cancer. Associations for cell surface or synaptic antibodies are more variable; some associate with cancer in over 50 percent of cases (eg, alpha-amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid [AMPA] receptor antibodies, gamma-aminobutyric acid type B [GABA-B] receptor antibodies), while others rarely do (eg, leucine-rich glioma inactivated 1 [LGI1] antibodies, contactin-associated protein-like 2 [Caspr2] antibodies). These syndromes are reviewed in more detail separately. (See "Paraneoplastic and autoimmune encephalitis".)

- **Brainstem encephalitis** – Brainstem encephalitis may present with a wide range of symptoms localizing to the midbrain, pons, and medulla, including extraocular movement deficits, opsoclonus, nystagmus, dysphagia, dysarthria, sensorineural deafness, trigeminal sensory loss, central hypoventilation, and vertigo. The term "rhombencephalitis" is sometimes used to denote inflammatory syndromes affecting the lower brainstem specifically. (See "Paraneoplastic and autoimmune encephalitis", section on 'Brainstem encephalitis'.)

- **Rapidly progressive cerebellar syndrome** – Some paraneoplastic disorders produce a rapidly progressive cerebellar syndrome with symptoms of limb, truncal, and gait ataxia; nystagmus; and dysarthria leading to severe disability in less than three months. Symptoms occasionally begin unilaterally or have a more insidious course. In other cases, cerebellar symptoms are just one component of a broader syndrome of encephalitis or encephalomyelitis. (See "Paraneoplastic and autoimmune encephalitis", section on 'Specific antibody-associated syndromes'.)

- **Encephalomyelitis** – Patients with encephalomyelitis present with symptoms that implicate multiple sites in the nervous system, including temporal-limbic regions, brainstem, cerebellum, spinal cord, dorsal root ganglia, and peripheral nervous system. (See "Paraneoplastic and autoimmune encephalitis", section on 'Encephalomyelitis'.)

- **Myelitis** – Myelitis (or myelopathy) is characterized by progressive spastic paresis and bladder dysfunction due to involvement of the spinal cord. In paraneoplastic disorders, myelitis usually occurs in association with involvement of other areas of the nervous system (ie, encephalomyelitis). However, rare cases of isolated paraneoplastic myelopathy are observed. (See "Paraneoplastic syndromes affecting spinal cord, peripheral nerve, and muscle", section on 'Myelopathy'.)

- **Motor neuronopathy** – Motor neuronopathy refers to dysfunction of the anterior horn cells, resulting in isolated lower motor neuron weakness and atrophy in the arms and legs. (See "Paraneoplastic syndromes affecting spinal cord, peripheral nerve, and muscle", section on 'Subacute motor neuronopathy'.)

- **Stiff-person syndrome** – Stiff-person syndrome is characterized by progressive muscle stiffness, rigidity, and spasms predominantly involving the axial muscles of the trunk and proximal muscles of the limbs. A related disorder is called progressive encephalomyelitis with rigidity and myoclonus (PERM), in which patients develop distal limb rigidity along with brainstem dysfunction, seizures, or encephalopathy. Most cases of stiff-person syndrome are not associated with a tumor or cancer, although paraneoplastic cases do occur. (See "Paraneoplastic syndromes affecting spinal cord, peripheral nerve, and muscle", section on 'Stiff-person syndrome'.)

- **Opsoclonus-myoclonus** – Opsoclonus-myoclonus syndrome is characterized by spontaneous, arrhythmic, multidirectional saccadic eye movements along with diffuse or focal body myoclonus and truncal titubation. Many patients also have ataxia and other cerebellar signs, and some have encephalopathy. In children, opsoclonus-myoclonus is symptomatic of neuroblastoma in approximately half of cases. In adults, small cell lung cancer (SCLC) or other malignancies are identified in 20 to 40 percent of cases. (See "Opsoclonus-myoclonus syndrome", section on 'Clinical features'.)

Peripheral nervous system — Paraneoplastic syndromes affecting the peripheral nervous system are organized by anatomy:

- **Sensory neuronopathy** – Paraneoplastic involvement of the dorsal root ganglia results in subacute sensory neuronopathy, with loss of vibratory sensation and joint position sense, sensory ataxia, and impaired pain and temperature sensation. The neuronopathy often precedes a cancer diagnosis and may progress to involve other

areas of the nervous system. (See "Paraneoplastic syndromes affecting spinal cord, peripheral nerve, and muscle", section on 'Subacute sensory neuronopathy'.)

- **Peripheral neuropathies** – A variety of peripheral neuropathies have been described as paraneoplastic syndromes, including an acute sensorimotor radiculoneuropathy that is clinically identical to Guillain-Barré syndrome, chronic sensorimotor neuropathy, neuropathies associated with lymphoproliferative disorders, autonomic neuropathy (usually in combination with other areas of nervous system involvement), and multifocal mononeuropathy due to vasculitic neuropathy. (See "Paraneoplastic syndromes affecting spinal cord, peripheral nerve, and muscle", section on 'Peripheral nerve'.)

  Of note, recurrent gastrointestinal pseudo-obstruction (enteric neuropathy) can represent a paraneoplastic autonomic neuropathy related to myenteric plexus dysfunction, typically associated with anti-Hu antibodies. By contrast, antibodies against ganglionic acetylcholine receptor are more commonly seen in nonparaneoplastic cases. (See "Chronic intestinal pseudo-obstruction: Etiology, clinical manifestations, and diagnosis", section on 'Paraneoplastic'.)

- **Neuromuscular junction disorders** – Antibodies directed against voltage-gated calcium channels in presynaptic nerve terminals result in Lambert-Eaton myasthenic syndrome (LEMS), which represents a paraneoplastic disorder in approximately 50 percent of cases. Patients present with proximal muscle weakness, autonomic dysfunction, and variable cranial nerve involvement. (See "Lambert-Eaton myasthenic syndrome: Clinical features and diagnosis", section on 'Clinical features'.)

  Myasthenia gravis (MG), a postsynaptic neuromuscular junction disorder often associated with antibodies against the acetylcholine receptor, is a paraneoplastic manifestation of a thymic tumor in approximately 10 percent of cases. Patients present with varying combinations of ptosis, diplopia, bulbar symptoms (eg, dysarthria, dysphagia, fatigable chewing), and skeletal muscle weakness. (See "Clinical manifestations of myasthenia gravis", section on 'Clinical features'.)

- **Muscle syndromes** – Paraneoplastic syndromes involving muscle include dermatomyositis, acute necrotizing myopathy, and neuromyotonia (peripheral nerve hyperexcitability, or Isaacs syndrome). Nerve hyperexcitability in combination with encephalopathy and sleep disorders (Morvan syndrome) can also be seen. Clinical features of each disorder are reviewed separately. (See "Paraneoplastic syndromes affecting spinal cord, peripheral nerve, and muscle", section on 'Muscle function' and "Paraneoplastic and autoimmune encephalitis", section on 'Anti-Caspr2 associated encephalitis'.)

Visual syndromes — Altered vision can result from a paraneoplastic syndrome affecting the retina, the uvea, or the optic nerve.

- **Retinopathy** – Cancer-associated retinopathy is a paraneoplastic syndrome characterized by photosensitivity, abnormal visual acuity, color vision abnormalities, scotomas, and poor night vision. A variety of antiretinal antibodies may be present in serum. A similar syndrome can occur in patients with melanoma and is also associated with a variety of antibodies that react with the bipolar cells of the retina. (See "Paraneoplastic visual syndromes", section on 'Cancer-associated retinopathy' and "Paraneoplastic visual syndromes", section on 'Melanoma-associated retinopathy'.)

- **Uveal melanocytic proliferation** – Rare patients with cancer develop bilateral diffuse uveal melanocytic proliferation causing vison loss, retinal detachment, and rapid cataract formation. Autoantibodies have not been identified, but a serum-bound protein that stimulates melanocytic proliferation in vitro has been described in some patients. (See "Paraneoplastic visual syndromes", section on 'Bilateral diffuse uveal melanocytic proliferation'.)

- **Optic neuropathy** – Optic neuropathy manifests with painless visual loss and optic disc edema. Most cases of paraneoplastic optic neuropathy occur in association with additional areas of involvement, such as encephalomyelitis, retinitis, or sensorimotor neuropathy. (See "Paraneoplastic visual syndromes", section on 'Optic neuropathy'.)

DIAGNOSTIC EVALUATION

The differential diagnosis of paraneoplastic neurologic disorders is wide and requires the reasonable exclusion of alternative causes. Many paraneoplastic syndromes develop in the early stages of cancer, and the presence of a tumor or tumor recurrence can be difficult to demonstrate. The detection of neuronal antibodies can be very helpful for diagnosis and can guide the search for a tumor. However, while some antibodies have a strong association with the presence of a cancer, other antibodies can be found in patients with or without cancer (table 2).

Diagnostic criteria — Initial diagnostic criteria developed in 2004 divided patients with suspected paraneoplastic syndromes into "definite" and "possible" categories [40]. These criteria were updated in 2021 and now include three levels of evidence for the diagnosis of a definite, probable, or possible paraneoplastic neurologic syndrome [39].

The diagnostic level of certainty is based on clinical phenotype, type of antibody, presence or absence of cancer, and time of follow-up. Follow-up time is particularly relevant for those

patients whose initial tumor screening is negative since the likelihood of a paraneoplastic etiology decreases as time elapses with no neoplasm identified.

The criteria recognize specific clinical presentations that almost always have a paraneoplastic etiology. These syndromes are defined as "high-risk phenotypes" and are often referred to as classical paraneoplastic neurologic syndromes [40]. Patients presenting with any of these syndromes should undergo screening for a tumor. (See 'Search for occult malignancy' below.)

High-risk syndromes include (see 'Clinical syndromes' above):

- Encephalomyelitis
- Limbic encephalitis
- Rapidly progressive cerebellar syndrome
- Opsoclonus-myoclonus
- Sensory neuronopathy
- Gastrointestinal pseudo-obstruction (enteric neuropathy)
- Lambert-Eaton myasthenic syndrome (LEMS)

Neurologic syndromes that can occur with or without cancer are defined as "intermediate-risk phenotypes." Recognition of these syndromes should raise concern for a paraneoplastic etiology, especially when no alternative explanation is found. A paraneoplastic etiology of an intermediate-risk phenotype should always be considered when the onset is rapidly progressive (<3 months) or there are inflammatory findings in the cerebrospinal fluid (CSF) or brain/spinal magnetic resonance imaging (MRI).

Intermediate-risk syndromes include:

- Encephalitis other than well-defined limbic encephalitis, when criteria for possible autoimmune encephalitis are fulfilled (table 4)
- Anti-N-methyl-D-aspartate (anti-NMDA) receptor encephalitis (table 5)
- Brainstem encephalitis
- Morvan syndrome
- Isolated myelopathy
- Stiff-person syndrome
- Polyradiculoneuropathies, especially axonal pattern and concurrent central nervous system involvement

In the updated criteria, the neuronal autoantibodies are divided into three categories based on the frequency of a cancer association (table 2). High-risk antibodies are those that in >70 percent of cases are cancer associated. These antibodies include the classic paraneoplastic/onconeuronal antibodies described above and in the table (table 2) (see

'Types of antibodies' above). Intermediate-risk antibodies are associated with cancer in 30 to 70 percent of cases, and lower-risk antibodies are cancer associated in <30 percent of cases (table 2).

For some antibodies, such as contactin-associated protein-like 2 (Caspr2), the cancer risk level changes based on the clinical syndrome. Thus, 50 percent of patients with Caspr2 antibodies and Morvan syndrome have a tumor (usually thymoma), while less than 30 percent of patients with these antibodies and limbic encephalitis have thymoma.

Antibody screening — Patients with suspected paraneoplastic neurologic syndromes should have antibody screening performed on both serum and CSF, whenever possible. Differences in sensitivity between compartments vary by the type of antibody, as discussed below. (See 'Interpretation' below.)

Clinical testing may be performed on-site in some large centers or as a send-out to a larger clinical or commercial laboratory. There are important limitations to clinical testing in certain situations, and clinicians should have a low threshold to repeat testing in a research laboratory when there is a mismatch between clinical suspicion and antibody testing results.

Testing methods — The gold-standard detection method for most neuronal antibodies is rodent brain tissue immunohistochemistry/immunofluorescence accompanied by confirmatory studies using either immunoblot with recombinant proteins (for most antibodies directed toward intracellular antigens) or cell-based assays (for antibodies against cell surface or synaptic proteins) [39].

Despite this gold standard, very few laboratories use both techniques. Commercial kits testing multiple antibodies typically consist of immunoblots and cell-based assays. While these can be useful for initial screening, the risk of false-positive and false-negative results is higher compared with gold-standard methods. In addition, kits often include testing for antibodies of limited clinical value along with testing for validated antibodies with well-known clinical and cancer associations.

When there are concerns about false-negative or false-positive results, confirmatory tissue-based testing can be requested in some clinical laboratories, or samples can be reassessed in a research laboratory.

Interpretation — Important tenets of antibody screening include:

- **Prevalence in serum versus CSF** – The existence of antibodies in serum and CSF varies across paraneoplastic disorders.
    - Antibodies against intracellular antigens (most classical paraneoplastic/onconeuronal antibodies) are almost always detectable in serum

(table 2). It is rare to find these antibodies in CSF when they are not detected in serum [41-43]. (See 'Types of antibodies' above.)

- Antibodies to cell surface or synaptic proteins (those that associate with encephalitis with or without a cancer association) frequently occur only in CSF, or the serum may give misleading results. For these antibodies, it is particularly important to test both serum and CSF. CSF should be included in the analysis. Further guidance on antibody testing in patients with encephalitis syndromes is provided separately. (See "Paraneoplastic and autoimmune encephalitis", section on 'Diagnostic approach'.)

- **Strength of neoplastic associations** – For some antibodies, there is a tight association between the antibody and a characteristic syndrome, yet the antibody does not differentiate between paraneoplastic and nonparaneoplastic cases. This is the case for P/Q type voltage-gated calcium channel antibodies in patients with LEMS, acetylcholine receptor antibodies in myasthenia gravis (MG), and most encephalitis syndromes related to neuronal cell surface and synaptic antibodies [14,44,45].

  Other antibodies are more informative in terms of the likelihood of an underlying cancer or tumor. As an example, in the context of stiff-person syndrome, patients with glutamic acid decarboxylase (GAD) antibodies rarely have cancer, while patients with amphiphysin antibodies usually have an underlying tumor [46,47]. (See "Stiff-person syndrome".)

- **Specificity and clinical significance** – Classical paraneoplastic antibodies are sometimes found in patients with cancer but without neurologic symptoms (usually in lower titers) [27,48,49] and in patients with neurologic disorders without an identifiable cancer [50]. However, these antibodies (table 2) rarely, if ever, occur in healthy individuals [51-53]. The presence of these antibodies should demand a careful search for an underlying neoplasm. (See 'Search for occult malignancy' below.)

  The specificity and clinical significance of antibodies against neuronal cell surface or synaptic proteins are reviewed in more detail separately. (See "Paraneoplastic and autoimmune encephalitis".)

- **Occurrence of multiple antibodies** – Several paraneoplastic antibodies (well and/or partially characterized) may co-occur in the same patient, particularly if the underlying tumor is small cell lung cancer (SCLC) [54,55]. In some cases, detection has clinical implications for a more treatable disorder.

  As an example, patients with SCLC and paraneoplastic cerebellar degeneration develop LEMS more frequently than expected [56]. Since the development of both disorders is highly disabling and LEMS usually responds to treatment, all patients with SCLC who

develop paraneoplastic cerebellar symptoms should be examined for LEMS. In almost all patients with LEMS, lower extremity reflexes are absent; sometimes they reappear after exercise. Another association is the development of LEMS in approximately 6 percent of patients with anti-Hu-associated paraneoplastic encephalomyelitis [57]. (See "Lambert-Eaton myasthenic syndrome: Clinical features and diagnosis".)

Other diagnostic tests — The diagnosis may be particularly difficult in patients who do not have a high-risk syndrome or when paraneoplastic antibodies are not detected. For all patients, the presumptive diagnosis of paraneoplasia requires the absence of metastatic and nonmetastatic complications that could explain the patient's symptoms, such as brain or leptomeningeal metastases and toxic effects of prior therapies.

Diagnostic tests that may be helpful for some paraneoplastic syndromes include:

Neuroimaging — Brain MRI can assist in the diagnosis of limbic encephalitis because the medial temporal lobes, the site of major pathology, often show increased signal on fluid-attenuated inversion recovery (FLAIR) images (image 1) and occasionally areas of contrast enhancement. Patients with paraneoplastic cerebellar degeneration may develop signs of atrophy detectable by MRI several months after the onset of symptoms [56,58]; however, for most paraneoplastic syndromes, neuroimaging studies are normal or nonspecific.

Positron emission tomography (PET) of the brain using fluorodeoxyglucose (FDG-PET) will occasionally identify hypermetabolism of the medial temporal lobe(s) in patients with limbic encephalopathy [59], or of the cerebellum in patients with paraneoplastic cerebellar degeneration [60].

Lumbar puncture — Although detection of classical paraneoplastic antibodies in CSF confirms that the disorder is paraneoplastic, in our experience these antibodies are usually present in the serum as well, except in some patients with anti-Tr antibodies [41,43]. By contrast, CSF examination is critical in patients suspected of having antigens to neuronal cell surface or synaptic proteins (eg, anti-NMDA receptor encephalitis) because serum testing may be negative, and antibody titers are higher in CSF than in serum [61]. (See 'Antibody screening' above.)

CSF examination can assist in making the diagnosis of paraneoplastic syndromes in two other ways:

- The combination of negative cytology for malignant cells and the absence of meningeal enhancement on MRI can reasonably exclude leptomeningeal metastases.
- Inflammatory changes (eg, pleocytosis, intrathecal synthesis of immunoglobulin G [IgG], oligoclonal bands) can support the presence of an inflammatory or immune-mediated neurologic disorder [62].

Electrophysiology — Some paraneoplastic syndromes of the peripheral nervous system are associated with characteristic electrophysiologic findings. These include LEMS, MG, neuromyotonia, and dermatomyositis. However, these findings are also present when the same neurologic syndrome is not associated with a tumor. Nevertheless, electrophysiologic findings that confirm the underlying syndrome may still be helpful by directing the search for the neoplasm to specific organs (eg, lung with LEMS and thymus with MG).

Search for occult malignancy — While paraneoplastic syndromes are most often diagnosed in the setting of a known malignancy, it is common for a paraneoplastic disorder to develop before a cancer is identified. Clinical experience and the literature suggest that the large majority of tumors will be diagnosed within two years of the onset of the neurologic disorder [39].

The clinical syndrome and identification of certain paraneoplastic antibodies may suggest a specific underlying tumor and direct investigations (table 2). In most other instances, the tumor is revealed by computed tomography (CT) of the chest, abdomen, and pelvis. Additional tests, such as mammogram, breast MRI, or ultrasound of the pelvis or testes, are ordered when suggested by the clinical syndrome and identification of certain paraneoplastic antibodies or the presence of other risk factors (table 6).

Whole-body FDG-PET combined with CT is useful in demonstrating occult neoplasms or small metastatic lesions and is a reasonable alternative to sequential testing starting with CT and mammography [63-65]. In one case series of 104 patients, sensitivity and specificity of FDG-PET were 80 and 67 percent, respectively, compared with 30 and 71 percent for CT [66]. Results from another small study found that FDG-PET combined with CT scanning increased sensitivity and accuracy of tumor diagnosis in patients with paraneoplastic syndromes [67].

A negative PET/CT scan does not rule out underlying cancer; use of other imaging modalities (eg, MRI, ultrasound) or repeating PET/CT scan after a several-month interval can be fruitful. A 2010 taskforce recommended repeat cancer screening three to six months after an initial negative evaluation, followed by screening every six months up until four years if testing remains unrevealing [68]. In LEMS, screening for two years is sufficient. Also, if an identified cancer is not consistent with the paraneoplastic syndrome or the identified antibody, continued search for another neoplasm should be considered [69].

TREATMENT AND PROGNOSIS

Because the majority of neurologic paraneoplastic syndromes are immune mediated, two general approaches to therapy have been tried: removal of the antigen source by treatment of the underlying tumors, and suppression of the immune response. The likelihood of response varies by syndrome; additional predictors of response are not well understood.

In general, in the paraneoplastic disorders with antibodies against intracellular antigens (classical paraneoplastic or onconeuronal antibodies), in which the underlying pathogenic mechanism is thought to be cytotoxic T cell mediated, the response to treatment (antitumor plus immunotherapy) is less satisfactory than in those disorders associated with antibodies against neuronal cell surface or synaptic proteins, in which the pathogenic mechanism is antibody mediated.

- **Syndromes likely to respond to treatment** – Immunomodulation or suppression is beneficial for some conditions, such as the Lambert-Eaton myasthenic syndrome (LEMS) and myasthenia gravis (MG). In these conditions, plasma exchange or intravenous immune globulin (IVIG; eg, 0.4 g/kg daily for five days) is usually effective in improving the neurologic status, at least in the short term. (See "Lambert-Eaton myasthenic syndrome: Treatment and prognosis".)

  Encephalitides associated with antibodies against neuronal cell surface antigens or synaptic proteins such as the N-methyl-D-aspartate (NMDA), alpha-amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid (AMPA), or gamma-aminobutyric acid type B (GABA-B) receptors, and leucine-rich glioma inactivated 1 (LGI1), among others, are also fairly responsive to immunosuppressive therapies. These disorders are usually treated with intravenous methylprednisolone, IVIG, or plasma exchange. If these fail, rituximab and/or cyclophosphamide are often effective. For patients that are severely affected, consideration can be given to starting rituximab as part of the initial therapeutic regimen. (See "Paraneoplastic and autoimmune encephalitis", section on 'Treatment and prognosis'.)

- **Syndromes that may respond to treatment** – Although most patients with paraneoplastic peripheral neuropathies do not have paraneoplastic antibodies, there is often evidence of inflammatory mechanisms likely related to an immune-mediated etiology, such as cerebrospinal fluid (CSF) pleocytosis, increased CSF proteins, or the presence of inflammatory infiltrates on nerve biopsy. For peripheral neuropathies, and particularly those with predominant demyelinating features, plasmapheresis, IVIG, and rituximab can be effective.

  In cancer-associated disorders that are probably antibody mediated, such as opsoclonus-myoclonus [70], stiff-person syndrome [71], and dermatomyositis [72], the approach to treatment is usually similar to that used for syndromes associated with antibodies against cell surface antigens. (See "Opsoclonus-myoclonus syndrome" and "Stiff-person syndrome" and "Initial treatment of dermatomyositis and polymyositis in adults".)

- **Syndromes that usually do not respond to treatment** – These include most of the paraneoplastic syndromes associated with classic paraneoplastic antibodies that target

intracellular antigens, such as paraneoplastic cerebellar degeneration, encephalomyelitis, the subgroup of limbic encephalitis with classic paraneoplastic antibodies to intracellular antigens, myelitis, and cancer-associated retinopathy. In these patients, the treatment approach of removing the antibodies from serum (eg, plasma exchange, IVIG) usually fails; immunotherapies addressing T cell mechanisms should be considered early (eg, cyclophosphamide or rituximab, which decreases B cell antigen presentation to T cells) [73]. Prompt control of the tumor and use of immunotherapy may stabilize symptoms or result in partial improvement [74], but rarely to the degree seen in disorders associated with antibodies against cell surface or synaptic proteins.

Across the spectrum of paraneoplastic syndromes, there is some evidence that prompt oncologic treatment and immunotherapy (immunomodulation, immunosuppression) can be beneficial, especially if instituted during the time of symptom progression rather than after deficits have been fully established [73,75,76]. The failure of the neurologic syndrome to respond to treatment may be due to irreversible neuronal damage that occurred before the diagnosis was made and treatment begun. Rare patients may develop a second paraneoplastic syndrome after recovering or stabilizing from the first. In one case series of eight such patients, the second paraneoplastic syndrome revealed cancer relapse in five and a second cancer in one patient [77].

SUMMARY AND RECOMMENDATIONS

- **Definition** – Paraneoplastic neurologic syndromes are a heterogeneous group of disorders caused by mechanisms other than metastases, metabolic and nutritional deficits, infections, coagulopathy, or side effects of cancer treatment. These syndromes may affect any part of the nervous system, from cerebral cortex to neuromuscular junction and muscle (table 1). (See 'Introduction' above.)

- **Pathogenesis** – Paraneoplastic neurologic syndromes are believed to result when an immunologic response is directed against shared antigens that are ectopically expressed by the tumor but otherwise predominantly expressed by the nervous system. Antibodies can be detected in the serum or cerebrospinal fluid (CSF) of many, but not all, patients with paraneoplastic syndromes. (See 'Pathogenesis' above.)

- **Clinical syndromes** – Paraneoplastic syndromes may affect any part of the nervous system, from cerebral cortex to neuromuscular junction and muscle (table 1). Some syndromes affect a single area, such as the anterior horn cell in motor neuronopathy. Others affect multiple areas, as in the case of encephalomyelitis. (See 'Clinical syndromes' above.)

- **Diagnostic evaluation** – Patients suspected of having a paraneoplastic neurologic syndrome should be tested for paraneoplastic antibodies in both serum and CSF. Testing in both compartments is especially important for some autoimmune encephalitides associated with antibodies against neuronal cell surface or synaptic proteins. (See 'Diagnostic criteria' above.)

  Important caveats include the following (see 'Antibody screening' above):

  - Low levels of some paraneoplastic antibodies may be seen in the serum of cancer patients without paraneoplastic syndromes.
  - Well-characterized paraneoplastic antibodies rarely, if ever, occur in healthy individuals. The presence of such antibodies should demand a careful search for an underlying neoplasm.
  - Some but not all paraneoplastic antibodies may be associated with different neurologic syndromes, and the same neurologic syndrome may be associated with different paraneoplastic antibodies.

- **Additional tests** – Neuroimaging studies, lumbar puncture, and electrophysiology tests can be helpful in characterizing the neurologic syndrome. (See 'Other diagnostic tests' above.)

- **Detection of malignancy** – The paraneoplastic syndrome may precede the diagnosis of underlying malignancy. In such cases, the clinical syndrome and identification of certain paraneoplastic antibodies may suggest a specific underlying tumor and direct investigations (table 6 and table 2). (See 'Search for occult malignancy' above.)

- **Treatment** – Two general approaches to treatment include removal of the antigen source by treatment of the underlying tumor, and suppression of the immune response. The optimal treatment and likelihood of response vary depending on the specific disorder. (See 'Treatment and prognosis' above.)

Topic 5188 Version 32.0

GRAPHICS

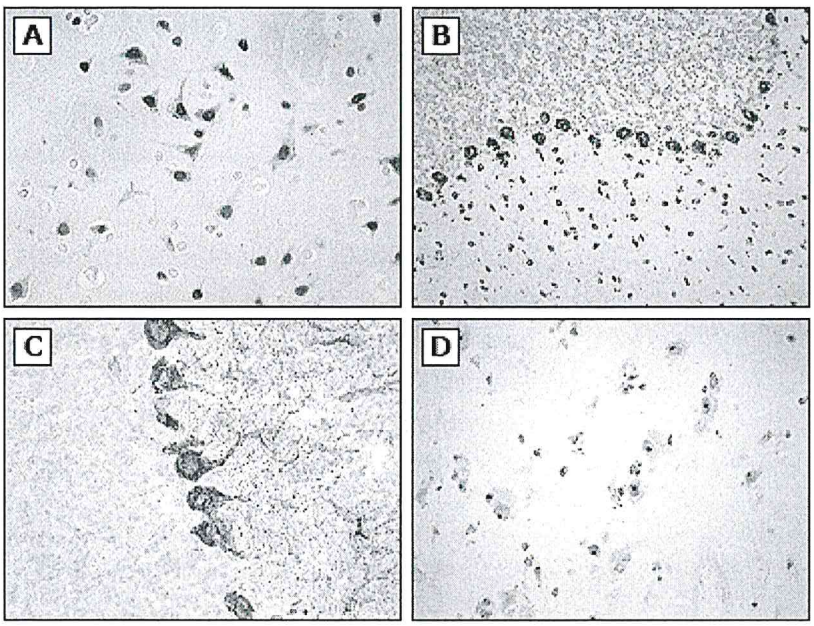
Paraneoplastic syndromes of the nervous system

Paraneoplastic syndromes of the central nervous system
Encephalomyelitis*
Myelitis*
Limbic encephalitis*
Brainstem encephalitis*
Cerebellar degeneration*
Opsoclonus myoclonus ataxia*
Visual syndromes
Cancer-associated retinopathy*
Melanoma-associated retinopathy*
Optic neuritis*
Necrotizing myelopathy
Motor neuron syndrome
Subacute motor neuronopathy
Other syndromes
Stiff-person syndrome*
Subacute sensory neuronopathy*
Paraneoplastic syndromes of the peripheral nervous system
Chronic sensorimotor neuropathy
Association with plasma cell dyscrasias
Acute sensorimotor neuropathy
Guillain-Barré syndrome
Plexitis (eg, brachial neuritis)
Autonomic neuropathy*
Vasculitis of nerve and muscle
Paraneoplastic syndromes of the neuromuscular junction and muscle
Myasthenia gravis*
Lambert-Eaton myasthenic syndrome*
Dermatomyositis
Neuromyotonia*
Acute necrotizing myopathy

* Syndromes in which specific paraneoplastic antibodies have been identified; the absence of antibodies does not exclude a paraneoplastic etiology.

Graphic 50304 Version 6.0

Reactivity of paraneoplastic antineuronal antibodies



Reactivity of different paraneoplastic antibodies with the nervous system.

(A) Reactivity of anti-Hu antibodies with human cerebral cortex. There is predominant staining of the nuclei of the neurons (with sparing of the nucleoli) and milder staining of the cytoplasm. Glial cells are not immunoreactive.

(B) Reactivity of anti-Yo antibodies with rat cerebellum. There is intense immunolabeling of the cytoplasm of the Purkinje cells and of neurons of the molecular layer.

(C) Reactivity of anti-Tr antibodies with rat cerebellum. There is a characteristic dot-like immunolabeling of the cytoplasm of Purkinje cells and the neuropil of the molecular layer of cerebellum.

(D) Reactivity of anti-Ma2 (Ta) antibodies with human cerebral cortex. This antibody reacts with the nucleoli of the neurons and shows mild immunolabeling of the cytoplasm; glial cells are not immunoreactive.

Courtesy of Josep Dalmau, MD, PhD.

Graphic 56327 Version 4.0

Antibodies associated with paraneoplastic neurologic syndromes

Antibody (alternative name)	Neurologic phenotypes	Frequency of cancer (%)	Usual tumors	Sex, age-related, and other specificities
High-risk antibodies (>70% associated with cancer)				
Hu (ANNA-1)	Sensory neuronopathy, chronic gastrointestinal pseudoobstruction, encephalomyelitis, limbic encephalitis	85	SCLC >> NSCLC, other neuroendocrine tumors, neuroblastoma	Limbic encephalitis is usually nonparaneoplastic in patients <18 years of age.
CV2/CRMP5	Encephalomyelitis, sensory neuronopathy	>80	SCLC, thymoma	Patients with an associated thymoma are younger and present more frequently with MG and less commonly with neuropathy.
SOX1	LEMS with and without rapidly progressive cerebellar syndrome	>90	SCLC	Stronger correlation with SCLC than with a particular neurologic presentation.
PCA-2 (MAP1B)	Sensorimotor neuropathy, rapidly progressive cerebellar syndrome, encephalomyelitis	80	SCLC, NSCLC, breast cancer	
Amphiphysin	Polyradiculopathy, sensory neuronopathy, encephalomyelitis, stiff-person syndrome	80	SCLC, breast cancer	Associated antibodies commonly coexist. Patients with isolated antiamphiphysin are more likely to be females with breast cancer and stiff-person syndrome.

Ri (ANNA-2)	Brainstem/cerebellar syndrome, opsoclonus-myoclonus syndrome	>70	Breast > lung (SCLC and NSCLC)	Breast cancer in females; lung cancer in males.
Yo (PCA-1)	Rapidly progressive cerebellar syndrome	>90	Ovarian cancer, breast cancer	Almost all female; in males, antigen expression by tumor should be proven.
Ma2 and/or Ma	Limbic encephalitis, diencephalitis, brainstem encephalitis	>75	Testicular cancer, NSCLC	Young males: testicular tumors and isolated Ma2 positivity; older patients: SCLC and both Ma1/2 positivity.
Tr (DNER)	Rapidly progressive cerebellar syndrome	90	Hodgkin lymphoma	
KLHL11	Brainstem/cerebellar syndrome	80	Testicular cancer	Young males.
Intermediate-risk antibodies (30 to 70% associated with cancer)				
AMPAR	Limbic encephalitis	>50	SCLC, malignant thymoma	Paraneoplastic origin is more likely when other onconeuronal antibodies co-occur.
$GABA_BR$	Limbic encephalitis	>50	SCLC	Paraneoplastic cases are more commonly observed in older males, in smokers, and in association with anti-KCTD16 antibodies. Most cases in young patients are not paraneoplastic.
mGluR5	Encephalitis	~50	Hodgkin lymphoma	
P/Q VGCC	LEMS, rapidly progressive cerebellar syndrome	50 (LEMS; nearly 90 for rapidly progressive	SCLC	Co-occurrence with N-type VGCC antibodies might be slightly more

		cerebellar syndrome)		common in paraneoplastic LEMS.
NMDAR	Anti-NMDAR encephalitis	38	Ovarian or extraovarian teratomas	Tumor (mostly ovarian teratomas) predominates in females 25 to 45 years of age (50%). Older patients less frequently have tumors (<25%), usually carcinomas. Paraneoplastic cases in children are very rare (<10%).
CASPR2	Morvan syndrome	50	Malignant thymoma	CASPR2 should be considered as an intermediate-risk antibody only in the setting of Morvan syndrome. When associated with other neurologic syndromes, the risk of cancer is very low.
Lower-risk antibodies (<30% associated with cancer)				
mGluR1	Cerebellar ataxia	30	Mostly hematologic	
$GABA_AR$	Encephalitis	<30	Malignant thymoma	Paraneoplastic origin is less frequent in children (10%) than in adults (60%).
CASPR2	Limbic encephalitis, acquired neuromyotonia (Isaac syndrome), Morvan syndrome	<30	Malignant thymoma	Morvan syndrome is more associated with malignant thymoma (~50%), whereas limbic encephalitis is almost always nonparaneoplastic.
GFAP	Meningoencephalitis	~20	Ovarian	May occur as an

			teratomas, adenocarcinomas	immunologic accompaniment in anti-NMDAR encephalitis with ovarian teratomas.
GAD65	Limbic encephalitis, stiff-person syndrome, cerebellar ataxia	<15	SCLC, other neuroendocrine tumors, malignant thymoma	Paraneoplastic origin more likely in older patients, males, and in association with neuronal antibodies or atypical clinical presentations.
LGI1	Limbic encephalitis	<10	Malignant thymoma, neuroendocrine tumors	Paraneoplastic cases are mainly observed in patients with Morvan syndrome and both serum LGI1 and CASPR2 antibodies.
DPPX	Encephalitis with CNS hyperexcitability, PERM	<10	B cell neoplasms	
GlyR	Limbic encephalitis, PERM	<10	Malignant thymoma, Hodgkin lymphoma	
AQP4	Neuromyelitis optica spectrum disorder	<5	Adenocarcinomas	Paraneoplastic origin associated with older age, male sex, and severe nausea/vomiting at onset.
MOG	MOG antibody-associated disease	5 cases reported	Mostly ovarian teratomas	

ANNA: antineuronal nuclear antibody; SCLC: small cell lung cancer; NSCLC: non-small cell lung cancer; CRMP5: collapsin-responsive mediator protein 5; MG: myasthenia gravis; SOX1: SRY-box transcription factor 1; LEMS: Lambert-Eaton myasthenic syndrome; PCA: Purkinje cell antibody; MAP1B: microtubule-associated protein 1B; DNER: delta/notch-like epidermal growth factor-related receptor; KLHL11: Kelch-like protein 11; AMPAR: α-amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid receptor; $GABA_BR$: gamma-aminobutyric acid-B receptor; KCTD16: potassium channel tetramerization domain containing; mGluR5: metabotropic glutamate

receptor 5; P/Q VGCC: P/Q type voltage-gated calcium channel; NMDAR: N-methyl-D-aspartate receptor; CASPR2: contactin-associated protein-like 2; mGluR1: metabotropic glutamate receptor 1; $GABA_AR$: gamma-aminobutyric acid-A receptor; GFAP: glial fibrillary acidic protein; GAD: glutamic acid decarboxylase; LGI1: leucine-rich glioma inactivated protein 1; DPPX: dipeptidyl-peptidase-like protein; CNS: central nervous system; PERM: progressive encephalomyelitis with rigidity and myoclonus; GlyR: glycine receptor; AQP4: aquaporin 4; MOG: myelin oligodendrocyte glycoprotein.

Adapted from: Graus F, Vogrig A, Muñiz-Castrillo S, et al. Updated diagnostic criteria for paraneoplastic neurologic syndromes. Neurol Neuroimmunol Neuroinflamm 2021; 8:e1014. Copyright © The Authors. Available at: https://nn.neurology.org/content/8/4/e1014.long (Accessed on March 28, 2022). Adapted under the terms of the Creative Commons Attribution License 4.0.

Graphic 135170 Version 1.0

Diagnostic criteria for definite autoimmune limbic encephalitis

All four of the following criteria must be met:*

1. Subacute onset (rapid progression of <3 months) of working memory deficits (short-term memory loss), seizures, or psychiatric symptoms suggesting involvement of the limbic system
2. Bilateral brain abnormalities on T2-weighted fluid-attenuated inversion recovery MRI highly restricted to the medial temporal lobes¶
3. At least one of the following:
   - CSF pleocytosis (>5 white blood cells per mm^3)
   - EEG with epileptic or slow-wave activity involving the temporal lobes
4. Reasonable exclusion of alternative causes

MRI: magnetic resonance imaging; CSF: cerebrospinal fluid; EEG: electroencephalogram.

* If one of the first three criteria is not met, a diagnosis of definite limbic encephalitis can be made only with the detection of antibodies against cell-surface, synaptic, or onconeural proteins.

¶ 18-fluorodeoxyglucose positron emission tomography (FDG-PET) can be used to fulfill this criterion and may be more sensitive than MRI for detecting medial temporal lobe abnormalities.

Graphic 111085 Version 2.0

Diagnostic criteria for possible autoimmune encephalitis

All three of the following criteria must be met:

1. Subacute onset (rapid progression of <3 months) of working memory deficits (short-term memory loss), altered mental status*, or psychiatric symptoms
2. At least one of the following:
   - New focal CNS findings
   - Seizures not explained by a previously known seizure disorder
   - CSF pleocytosis (>5 white blood cells per mm^3)
   - MRI features suggestive of encephalitis¶
3. Reasonable exclusion of alternative causes

CNS: central nervous system; CSF: cerebrospinal fluid; MRI: magnetic resonance imaging.

* Altered mental status defined as decreased or altered level of consciousness, lethargy, or personality change.

¶ Brain MRI hyperintense signal on T2-weighted fluid-attenuated inversion recovery (FLAIR) sequences highly restricted to one or both medial temporal lobes (limbic encephalitis), or in multifocal areas involving grey matter, white matter, or both, compatible with demyelination or inflammation.

Graphic 111084 Version 1.0

Diagnostic criteria for anti-NMDA receptor encephalitis

Probable anti-NMDA receptor encephalitis*
All three criteria must be met: 1. Rapid onset (<3 months) of at least four of the six following major groups of symptoms:¶ ▪ Abnormal (psychiatric) behavior or cognitive dysfunction ▪ Speech dysfunction ▪ Seizures ▪ Movement disorder, dyskinesias, or rigidity/abnormal postures ▪ Decreased level of consciousness ▪ Autonomic dysfunction or central hypoventilation 2. At least one of the following laboratory results: ▪ Abnormal EEG (focal or diffuse slow or disorganized activity, epileptic activity, or extreme delta brush) ▪ CSF with pleocytosis or oligoclonal bands 3. Reasonable exclusion of other disorders
Definite anti-NMDA receptor encephalitis*
1. IgG anti-GluN1 antibodies$^{\Delta}$ in the presence of one or more of the six major groups of symptoms, after reasonable exclusion of other disorders

NMDA: N-methyl-D-aspartate; EEG: electroencephalogram; CSF: cerebrospinal fluid; IgG: immunoglobulin G.

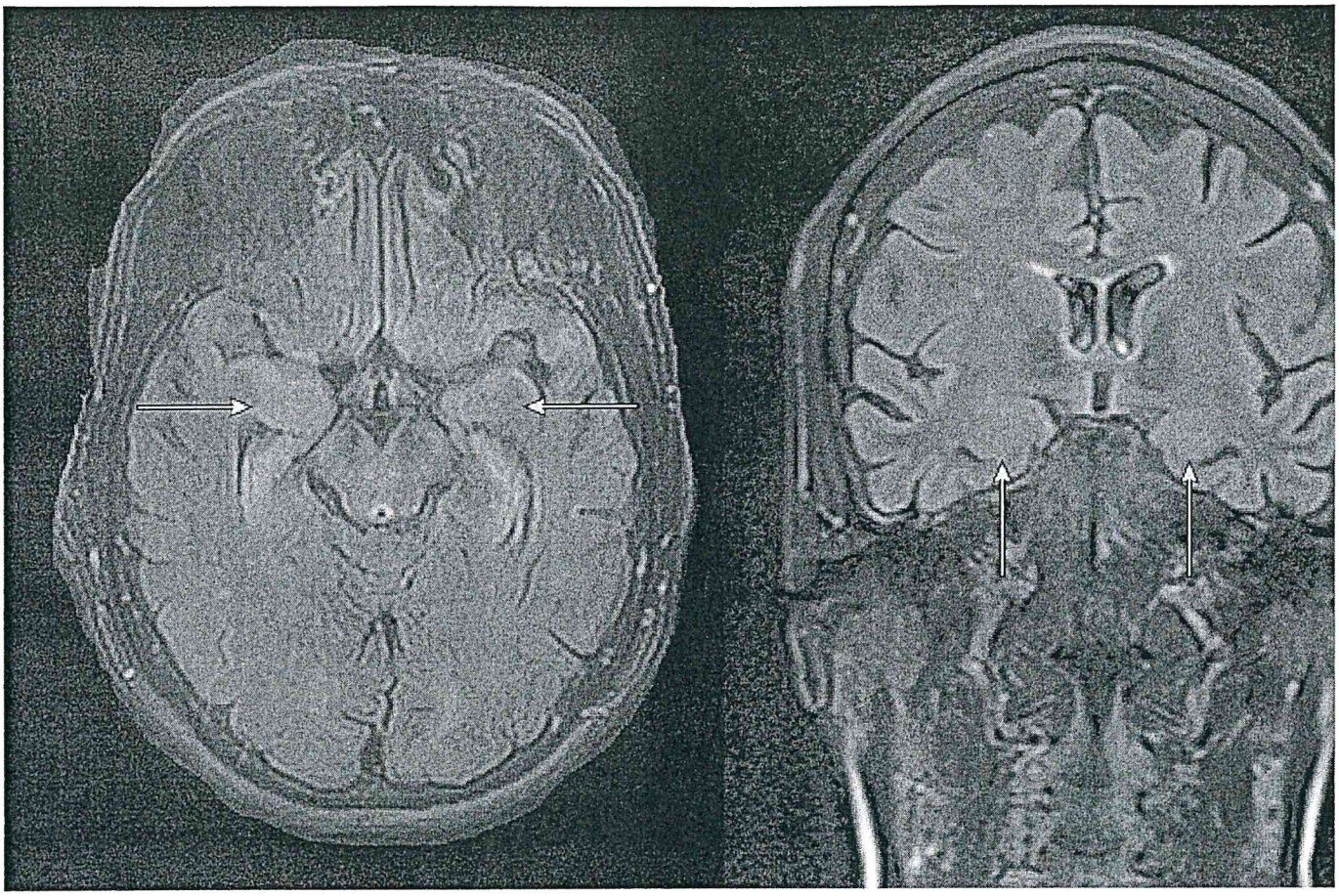
* Patients with a history of herpes simplex virus encephalitis in the previous weeks might have relapsing immune-mediated neurologic symptoms (post-herpes simplex virus encephalitis).

¶ In the presence of a systemic teratoma, diagnosis can be made in the presence of three groups of symptoms.

Δ Antibody testing should include testing of CSF. If only serum is available, confirmatory tests should be included (eg, live neurons or tissue immunohistochemistry), in addition to cell-based assay.

Graphic 111082 Version 1.0

Magnetic resonance imaging (MRI) in a patient with limbic encephalitis



Fifty-six-year-old female presenting with a 3-month history of faciobrachial dystonic seizures and progre mood and cognitive changes. Serum and CSF revealed anti-LGI1 antibodies. Axial and coronal MRI at init show increased fluid FLAIR signal abnormalities in the bilateral mesial temporal lobes (arrows).

CSF: cerebrospinal fluid; LGI1: leucine-rich glioma inactivated 1; MRI: magnetic resonance imaging; FLAI attenuated inversion recovery.

Graphic 111081 Version 2.0

Recommendations for oncologic screening in paraneoplastic neurologic syndromes according to the type of tumor or cancer suspected

Type of tumor or cancer suspected	Recommendations for oncologic screening
SCLC and malignant thymoma	CT chest ± FDG-PET/CT. For thymomas, chest MRI might be useful as well, especially in children.
Breast cancer	Mammography (breast US in young females and/or dense breast) ± breast MRI. If negative, FDG-PET/CT.
Ovarian teratoma	Transvaginal US (may not be feasible in young patients) ± MRI pelvis/abdomen. If negative, CT chest searching for extrapelvic teratomas.
Ovarian carcinoma	Transvaginal US ± MRI abdomen/pelvis or FDG-PET/CT. If negative, postmenopausal females with anti-Yo antibodies confirmed by 2 gold-standard techniques and a compatible neurologic phenotype should be considered for exploratory surgery or prophylactic bilateral hysterectomy and salpingo-oophorectomy.
Testicular tumors	US ± CT of the pelvic region; MRI might be an alternative to CT, especially in children. Orchiectomy is recommended in males <50 years old with microcalcifications on US, confirmed Ma2 antibodies, and a compatible neurologic phenotype. FDG-PET/CT is recommended when retroperitoneal or mediastinal germ cell tumors are suspected based on unremarkable testicular US or the detection of regressed tumors on testicular biopsy.
Hodgkin lymphoma	Full-body CT or FDG-PET/CT.
Neuroblastoma	CT ± MRI (CT is usually more sensitive since it identifies calcifications more easily, but MRI is preferred for staging of thoracic tumors); chest radiograph, abdominal US, and metabolic investigations lack sensitivity.
Unknown	Full-body CT followed, if negative, by FDG-PET/CT.

SCLC: small cell lung cancer; CT: computed tomography; FDG-PET: 18-F fluorodeoxyglucose positron emission tomography; MRI: magnetic resonance imaging; US: ultrasound.

Adapted from: Graus F, Vogrig A, Muñiz-Castrillo S, et al. Updated diagnostic criteria for paraneoplastic neurologic syndromes. Neurol Neuroimmunol Neuroinflamm 2021; 8:e1014. Copyright © The Authors. Available at: https://nn.neurology.org/content/8/4/e1014.long (Accessed on March 28, 2022). Adapted under the terms of the Creative Commons Attribution License 4.0.

Graphic 135171 Version 1.0

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