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CLINICAL PERSPECTIVE

Clinical approach to neurological paraneoplastic syndromes

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Abstract

Neurological paraneoplastic syndromes are immune-mediated disorders. The diagnosis of paraneoplastic syndromes is often difficult because they are rare and the onset of symptoms usually precedes detection of the underlying malignancy. Accurate diagnosis depends on recognition of the clinical phenotypes likely to be associated with a paraneoplastic aetiology and detection of an anti-neuronal antibody. Clinical phenotypes associated with a high risk of a paraneoplastic cause are limbic encephalitis, encephalomyelitis, rapidly progressive cerebellar syndrome, opsoclonus-myoclonus syndrome, subacute sensory neuronopathy, enteric neuropathy and Lambert Eaton myasthenic syndrome. Clinical phenotypes with an intermediate risk of a paraneoplastic aetiology are brainstem encephalitis, myelopathy, stiff person syndrome, Morvan syndrome and retinopathy. Anti-neuronal antibodies are extremely useful in the diagnosis of paraneoplastic neurological syndromes, but false-negative results can occur when only serum or cerebrospinal fluid (CSF) is tested. Commercial antibody panels do not include all antibodies associated with paraneoplastic syndromes, and if this diagnosis is strongly suspected, serum and CSF should be sent to a research laboratory. The risk of a false-positive result is increased if antibody tests are requested when there is a low pre-test probability of a paraneoplastic syndrome or if an antibody is detected in low titre.

Most non-metastatic effects of cancer on the nervous system have a readily identifiable cause: metabolic and nutritional disorders, vascular disease, infections and side effects of anti-neoplastic treatment. Other neurological disorders occur with increased frequency in patients with cancer, but the pathogenesis is less obvious. These have been called remote effects of cancer or paraneoplastic syndromes. In the past, various hypotheses were advanced to explain the link between paraneoplastic syndromes of the nervous system and malignancy: secretion of a neurotoxin by the cancer, competition between the tumour and the nervous system for an essential metabolite or an unidentified opportunistic infection. It is now recognised, however, that most neurological paraneoplastic syndromes are immune-mediated diseases resulting from an immune response directed against a neural antigen shared by the patient's tumour and the nervous system. Antibodies against intracellular antigens (e.g. Hu and Yo antibodies) are not pathogenic, but they are markers of a cytotoxic T-cell-mediated disorder. Antibodies against synaptic receptors and cell surface antigens such as the N-methyl-D-aspartate receptor (NMDAR) antibody are directly pathogenic and cause neuronal dysfunction by a variety of different mechanisms.[1,2]

The diagnosis of neurological paraneoplastic syndromes is challenging for several reasons:

1 They are rare. The incidence in population-based studies has varied between 2.6 and 8.9 per million person-years.[3–5] The different incidences in these studies are largely explained by different inclusion criteria. Paraneoplastic syndromes occur in one of 300 patients with cancer.[3]
2 The onset of neurological symptoms precedes diagnosis of the malignancy in more than 50% of cases.
3 When a patient is already known to have cancer, the paraneoplastic syndrome may be wrongly attributed to a metastatic or other non-metastatic effect of the malignancy.

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4 An identical clinicopathological syndrome can occur without an underlying malignancy.
5 The clinical manifestations are diverse because paraneoplastic syndromes can affect virtually any part of the nervous system.

Since neurological paraneoplastic syndromes usually present before the cancer is recognised, these patients are often referred to a neurologist or a general physician rather than an oncologist. Initial manifestations like orthostatic hypotension, gastrointestinal pseudo-obstruction, psychosis and other types of behavioural disturbance can bring these patients to the attention of other specialist physicians or psychiatrists.

Although they are rare, paraneoplastic syndromes are often considered in the differential diagnosis. What are the clues that an individual has a neurological paraneoplastic syndrome?

1 Most neurological paraneoplastic syndromes have an acute or subacute onset of symptoms over a few weeks or months or, occasionally, even a few days.
2 The course is rapidly progressive but may stabilise once the patient is severely disabled.
3 They cause severe disability.
4 Paraneoplastic syndromes affecting the central nervous system or the dorsal root ganglia are often associated with inflammatory changes in the cerebrospinal fluid (CSF): mild lymphocytic pleocytosis, increased protein concentration and oligoclonal bands.
5 Detection of an antibody against a neural antigen helps to determine that symptoms are due to a paraneoplastic syndrome, but indiscriminate use of antibody panels can lead to misdiagnosis.
6 Certain neurological disorders are more often paraneoplastic than others.

High- and intermediate-risk clinical phenotypes

In 2021, a panel of experts identified clinical phenotypes with a high or intermediate risk of a neurological paraneoplastic syndrome (Table 1).[6] High-risk phenotypes are frequently paraneoplastic and should automatically trigger a search for an underlying cancer. The patient's age and gender, the neurologic syndrome and the type of antibody help to determine the likely site of the cancer. Intermediate-risk phenotypes are less frequently paraneoplastic, but investigations looking for an underlying malignancy should be initiated if there is an acute or subacute onset of symptoms, inflammatory CSF abnormalities, a neuronal antibody is detected, and an alternative diagnosis is not found.

Table 1 High-risk and intermediate-risk phenotypes†

High risk
Limbic encephalitis
Encephalomyelitis
Rapidly progressive cerebellar syndrome
Opsoclonus-myoclonus
Sensory neuronopathy
Enteric neuronopathy
Lambert Eaton myasthenic syndrome
Intermediate risk
Encephalitis not restricted to limbic system
Brainstem encephalitis
Isolated myelopathy
Stiff person syndrome
Morvan syndrome

†Adapted from Graus *et al*.[6]

Encephalitis

The recognition and treatment of autoimmune encephalitis is a rapidly evolving field.[7] Many neuronal antibodies have been identified in patients with autoimmune encephalitis, some of which are paraneoplastic. Limbic encephalitis typically presents with rapidly progressive short-term memory impairment, epilepsy and psychiatric manifestations. About two-thirds have an abnormality in the limbic cortex on magnetic resonance imaging (MRI), and there may be a mild lymphocytic CSF pleocytosis.

Two classes of neuronal antibody have been detected in limbic encephalitis. One group reacts with intracellular antigens and is often associated with an underlying cancer: Hu antibody (ANNA1 or anti-neuronal nuclear antibody, type 1) with small-cell lung cancer and Ma2 antibody with testicular or non-small-cell lung tumours. While these antibodies are useful biomarkers of a paraneoplastic syndrome, they are not pathogenic. Instead, these paraneoplastic syndromes are T-cell-mediated disorders, which have a poor prognosis, even after immunosuppressive therapy and treatment of the malignancy. Other patients with limbic encephalitis have an anti-neuronal antibody that recognises a cell surface antigen. These antibodies are involved in the pathogenesis of the disease, and the patient often improves with treatment. Encephalitis associated with antibodies directed against a neuronal cell surface antigen may or may not be paraneoplastic (Table 2).

Two antibodies associated with autoimmune encephalitis have distinctive clinical and neuroimaging features. Anti-N-methyl-D-aspartate receptor (anti-NMDAR) encephalitis characteristically presents with striking psychiatric manifestations followed by seizures, movement disorders, memory impairment and autonomic instability. Anti-NMDAR encephalitis can develop in males and females of all ages but most commonly occurs in young women. Up

Table 2 Antibodies associated with paraneoplastic encephalitis and encephalomyelitis

Antibody	Frequency of cancer (%)	Associated cancer	Clinical features
Hu (ANNA1)	85	SCLC	LE, SSN, encephalomyelitis
Ma2	>75	Testicular, NSCLC	LE, diencephalic, brainstem encephalitis
AMPAR	50–70	SCLC, malignant thymoma	LE
$GABA_bR$	50–70	SCLC, malignant thymoma	LE
mGluR5	50	Hodgkin lymphoma	Ophelia syndrome
NMDAR	35	Teratoma (usually ovarian)	Paraneoplastic mainly in females 12–45 years
CASPR2	30	Malignant thymoma	LE, neuromyotonia, neuropathic pain, Morvan syndrome
$GABA_aR$	<30	Malignant thymoma	Typical MR abnormality
GFAP	20	Ovarian teratoma, adenocarcinoma	Meningoencephalitis
GAD65	<15	SCLC, neuroendocrine	LE, Stiff person, cerebellar ataxia
LGI1	<10	Malignant thymoma	LE
DPPX	<10	B cell neoplasms	Encephalitis, CNS hyperexcitability diarrhoea, weight loss
GlyR	<10	Malignant thymoma, Hodgkin lymphoma	LE, PERM

AMPAR, α-amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid receptor; ANNA1, anti-neuronal nuclear antibody, type 1; CASPR2, contactin-associated protein-like 2; DPPX, dipeptidyl peptidase-like protein; $GABA_aR$, gamma aminobutyric acid a receptor; $GABA_bR$, gamma aminobutyric acid b receptor; GAD 65, glutamic acid decarboxylase 65; GFAP, glial fibrillary acidic protein; GlyR, glycine receptor; LE, limbic encephalitis; LGI1, leucine-rich, glioma-inactivated 1; mGluR5, metabotropic glutamate receptor, type 5; NMDAR, N-methyl-D-aspartate receptor; NSCLC, non-small-cell lung cancer; PERM, progressive encephalomyelitis with rigidity and myoclonus; SCLC, small-cell lung cancer; SSN, subacute sensory neuronopathy.

to 50% of young women with anti-NMDAR encephalitis have a teratoma, usually a benign ovarian teratoma. Gamma aminobutyric acid a receptor ($GABA_aR$) encephalitis typically presents with a severe seizure disorder, but it is distinguished by striking MRI abnormalities with multifocal cortical and subcortical lesions on T2-weighted and fluid-attenuated inversion recovery images (Fig. 1).

Encephalomyelitis

Paraneoplastic encephalomyelitis is almost always associated with small-cell cancers and the Hu, CV2/CRMP5 (collapsin response-mediator protein 5) or PCA-2/microtubule-associated protein (MAP1B) antibodies. It presents with multifocal disease in the brain and spinal cord, often with involvement of the dorsal root ganglia, autonomic nervous system, nerve roots and peripheral nerves. More than 50% of patients harbouring the Hu antibody have multifocal disease.[8] Anti-Hu encephalomyelitis can present with focal cortical lesions, epilepsia partialis continua and focal cortical signs (Fig. 2).

Rapidly progressive cerebellar syndrome

This syndrome is characterised by rapidly progressive gait, truncal and limb ataxia, dysarthria and nystagmus.

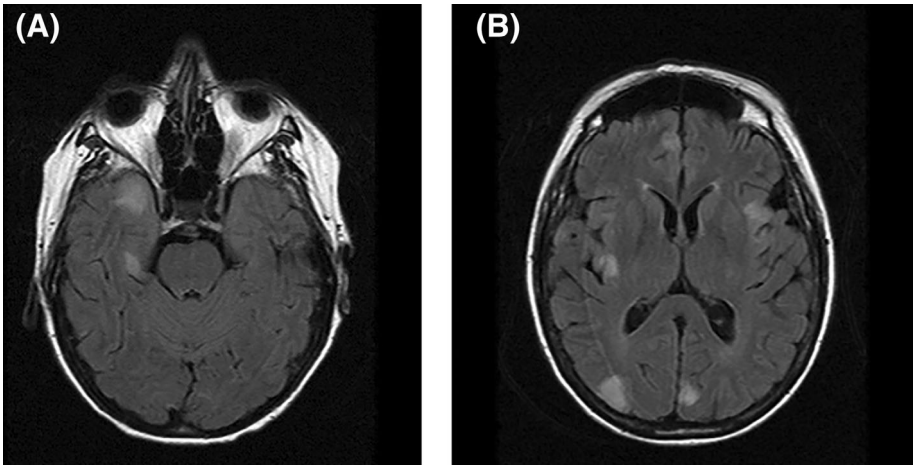

Figure 1 (A and B) Fluid-attenuated inversion recovery MRI in a woman with 10-day history of slurred speech, focal motor seizures in right face and tongue, malignant thymoma and $GABA_aR$ antibody in serum and CSF.

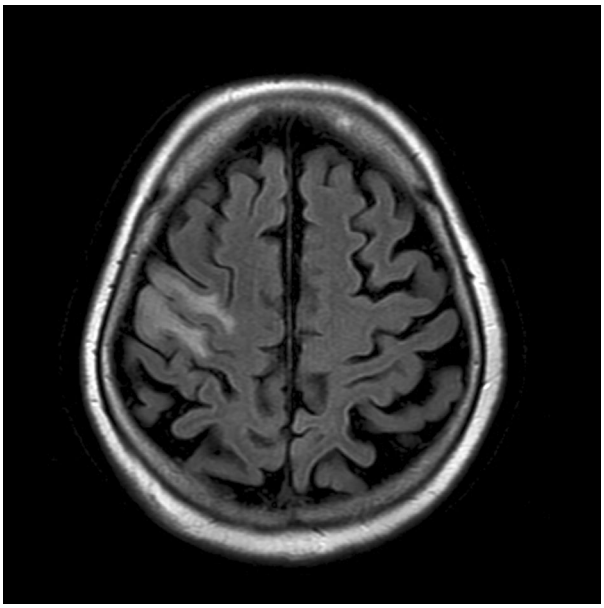

Figure 2 Fluid-attenuated inversion recovery MRI in a woman with epilepsia partialis continua, Hu antibody in serum and small cell lung cancer.

In the early stages, neuroimaging is normal, but cerebellar atrophy appears later.[9] The pathologic hallmark is a diffuse, severe loss of Purkinje cells. The most common antibodies associated with a pure cerebellar syndrome are anti-Yo (PCA1, Purkinje cell antibody, type 1) with ovarian or breast cancer and anti-Tr (delta notch-like epidermal growth factor-related antibody) in Hodgkin lymphoma. Several other antibodies have been found in a few isolated cases.

Opsoclonus-myoclonus

Opsoclonus is a striking disorder of eye movements with rapid, involuntary, multidirectional saccadic eye movements. It is associated with myoclonus, dysarthria, ataxia and encephalopathy. There are early-childhood and adult forms of the opsoclonus-myoclonus paraneoplastic syndrome. In children, it usually presents before the age of 2 years, and 50% have an underlying neuroblastoma. Opsoclonus and unsteady gait are commonly accompanied by irritability and disturbed sleep. Neuroimaging is usually normal in the early stages. There is a strong suspicion that the paraneoplastic opsoclonus-myoclonus syndrome in children is an immune-mediated disease, but a reproducible antibody or other biomarker has not been identified.[10] In adults, paraneoplastic opsoclonus-myoclonus is most frequently associated with small-cell lung and breast cancers. Patients with opsoclonus-myoclonus and breast cancer usually have the Ri antibody (anti-neuronal nuclear antibody, type-2 or ANNA2).[11] Patients with the Ri antibody also may have jaw dystonia and laryngospasm.

Sensory neuronopathy

The pathologic correlate of paraneoplastic sensory neuronopathy is inflammation and destruction of neurons in the dorsal root ganglia. The clinical picture is characterised by numbness and paraesthesia affecting the limbs, trunk and face.[12] There is loss of all sensory modalities including proprioception, sensory ataxia and areflexia, but power is normal unless dorsal root ganglionitis is part of a spectrum of encephalomyelitis with involvement of motor nerve roots and peripheral nerves. Nerve conduction studies show reduced or absent sensory nerve action potentials. Unlike most causes of sensory neuropathy, paraneoplastic sensory neuronopathy is distinguished by its rapidly progressive course, involvement of all sensory modalities and severe disability. The most common antibody is the Hu antibody in small-cell lung cancer followed by the CV2/CRMP5 antibody associated with small-cell cancer or thymoma and amphiphysin antibodies in small cell or breast cancer.

Gastrointestinal pseudo-obstruction

Dysfunction of the myenteric plexus presents with abdominal pain and distention, constipation and recurrent vomiting secondary to incomplete gastric emptying. It is often accompanied by other features of an autonomic neuronopathy, sensory neuronopathy and encephalomyelitis and usually occurs in the context of the Hu antibody.[13]

Lambert Eaton myasthenic syndrome[14]

Lambert Eaton myasthenic syndrome presents with gradual onset of weakness of pelvic and shoulder girdle muscles. Distal, bulbar and oculomotor muscles are affected late, if at all. Important clinical clues to the diagnosis are hyporeflexia, transient improvement in power and reflexes following repeated muscle contraction and autonomic symptoms especially dry mouth, erectile dysfunction and constipation. Nerve conduction studies show low-amplitude compound muscle action potentials which increase after exercise or high-frequency nerve stimulation. Fifty per cent of cases are associated with cancer, usually small-cell lung cancer. Most patients, whether paraneoplastic or non-paraneoplastic, have serum P/Q voltage-gated calcium channel antibodies.

Anti-glial nuclear (SOX1) antibodies are strongly associated with small-cell lung cancer, and their presence in a patient with Lambert Eaton myasthenic syndrome is a strong pointer to the paraneoplastic form of the disorder.

Brainstem encephalitis

Paraneoplastic brainstem encephalitis may be an isolated phenomenon or part of multifocal central nervous system disease. The isolated form is an intermediate-risk phenotype. Neuroimaging may or may not show signal change in the brainstem, but a normal MRI is a clue that a patient presenting with subacute onset of abnormal eye movements, dysarthria, dysphagia, ataxia and vertigo has paraneoplastic brainstem encephalitis. It is usually associated with an antibody directed against an intracellular antigen: Ma2, Hu or Ri. Brainstem encephalitis with the Ma2 antibody may be accompanied by limbic encephalitis and a diencephalic disorder manifesting with hypersomnolence, narcolepsy, hyperphagia and inappropriate antidiuretic hormone secretion. The Ma2 antibody is associated with testicular germ cell tumours or non-small-cell lung cancer.[15,16] Hu antibodies are usually associated with multifocal central and peripheral nervous system disease, but it can present with an isolated brainstem encephalitis, which typically involves the medulla manifesting with bulbar dysfunction and central hypoventilation.[17]

Myelopathy

An isolated myelopathy is an intermediate-risk phenotype which is usually associated with CV2/CRMP5 or amphiphysin antibodies and lung or breast cancer respectively. Symptoms can have a subacute or insidious onset. MRI scans show longitudinally extensive, symmetric T2 hyperintensities in white matter long tracts or in the grey matter of the spinal cord.[18]

Stiff person syndrome

Stiff person syndrome presents with stiffness and painful muscular spasms.[19] The non-paraneoplastic form is more common, mainly affects the legs and is associated with the glutamic acid decarboxylase 65 (GAD65) antibody. Paraneoplastic stiff person syndrome usually occurs in older patients, frequently affects the neck and arms and is usually associated with amphiphysin antibodies and breast cancer.

Morvan syndrome

This is a syndrome of peripheral nerve hyperexcitability with neuromyotonia, encephalopathy characterised by sleep disorder, hallucinations and abnormal behaviour, and autonomic dysfunction. Most cases have the contactin-associated protein-like 2 (CASPR2) antibody. Morvan syndrome can be non-paraneoplastic, but the paraneoplastic form is associated with malignant thymoma, sometimes with myasthenia gravis.[20]

Retinopathy

Paraneoplastic retinopathy was not included in the list of high- and intermediate-risk phenotypes by the panel in 2021, but the clinical features are sufficiently characteristic to describe it as a high- or intermediate-risk phenotype for a paraneoplastic aetiology. There are two forms of paraneoplastic retinopathy. The more common is carcinoma-associated retinopathy, which is associated with various types of malignancy and usually antedates recognition of the tumour. It presents with rapidly progressive, painless, bilateral visual loss with central or peripheral ring-like scotomata. Loss of vision is often preceded by night blindness and shimmering or flashing lights (photopsias). Initially, ophthalmoscopy is often unremarkable, but electroretinography shows absent or severely reduced cone- and rod-mediated responses. Carcinoma-associated retinopathy is believed to be a B-cell-mediated disorder. The most common associated antibody targets a protein in photoreceptor cells called recoverin. The other type of paraneoplastic retinopathy is melanoma-associated retinopathy. It usually presents after diagnosis of the melanoma with night blindness and photopsias. Loss of vision is usually much less severe than in carcinoma-associated retinopathy. Electroretinography shows reduced dark-adapted and light-adapted b waves, but normal a waves. A variety of antibodies reacting with melanoma and the retina have been reported in these patients.[21]

Myasthenia gravis and inflammatory myopathies

In about 15% of patients, myasthenia gravis is associated with thymoma and 30% of patients with thymoma develop myasthenia gravis. There is also an association between malignancy and dermatomyositis, but these conditions will not be discussed in this review.

Low-risk phenotypes

The clinical manifestations of neurological paraneoplastic syndromes are protean and distinguishing between a paraneoplastic syndrome and more common causes of a similar phenotype is often difficult.

Peripheral neuropathies

There are few clinical clues that distinguish a paraneoplastic disorder of spinal nerve roots and peripheral nerves from much more common causes of peripheral nerve disease, except that paraneoplastic neuropathies are often associated with involvement of the central nervous system. The most frequent antibodies are the CV2/CRMP5, amphiphysin and PCA2/MAP1B antibodies. The axonal polyradiculoneuropathy accompanying the CV2/CRMP5 antibody is typically asymmetric in onset and painful, while cerebellar ataxia, myelopathy and optic neuritis are common associated features. Small-cell cancers and thymoma are the most common malignancies.[22] PCA2/MAP1B antibodies are usually associated with small-cell cancers and peripheral neuropathy, but many patients also have cerebellar ataxia and encephalopathy. PCA2/MAP1B antibodies often coexist with other antibodies associated with small-cell cancer (Hu and CV2/CRMP5).[23]

Myeloneuropathy

Concomitant spinal cord and peripheral nerve disease is most commonly a metabolic, inflammatory, infectious, hereditary or toxic disorder, but a paraneoplastic aetiology should be considered when there is no other explanation. Amphiphysin, Hu and CV2/CRMP5 antibodies are most common and small-cell and breast cancers are the usual malignancies.[24]

Paraneoplastic neurologic syndrome clinical assessment and risk evaluation score

The panel of experts who updated the diagnostic criteria in 2021 developed a score to determine the likelihood an individual has a paraneoplastic syndrome when one is initially suspected. The score is based on the clinical phenotype, the type of antibody and the presence of cancer. When this score was retrospectively applied to a large cohort with a suspected neurological paraneoplastic syndrome, a score ≥6 (definite or probable paraneoplastic syndrome) had a sensitivity and specificity of 93% and 100% respectively.[25]

Antibodies and antibody testing

The accurate diagnosis of a neurological paraneoplastic syndrome relies on (i) the identification of a high- or intermediate-risk clinical phenotype and (ii) the detection of a neuronal antibody. The type of antibody predicts the likelihood and type of underlying malignancy. For example, the presence of the NMDAR antibody in a young woman with limbic encephalitis indicates there is a 50% or greater chance of an ovarian teratoma, but in a male or a young boy or girl there is unlikely to be a tumour.

The use of antibody testing comes with important caveats. A false-negative result is more likely when only serum or CSF is tested. For example, the NMDAR antibody is more likely to be found in the CSF than in serum, but leucine-rich, glioma inactivated 1 (LGI1) and CASPR2 antibodies are more often seen in serum. Therefore, both serum and CSF should be tested. Some well-characterised antibodies such as Kelch-like protein11 (KLHL11) and $GABA_aR$ antibodies, and rare or recently discovered antibodies' are not covered by commercial panels. If both serum and CSF are negative but there is high clinical suspicion of a paraneoplastic syndrome, samples should be sent to a laboratory specialising in the investigation of paraneoplastic syndromes.

The second problem is an increased risk of a false-positive result when there is a low pre-test probability of a neurological paraneoplastic syndrome. Several studies, including one from Australia, have shown that indiscriminate use of commercial paraneoplastic antibody testing kits yields a high frequency of false-positive results.[26–28] Most patients with a false-positive test did not have a high-risk clinical phenotype. Commercial line blot assays for Yo, Ma2, CV2/CRMP5 and SOX1 antibodies had a particularly high rate of false-positive results.[6] Paraneoplastic antibody panels usually should only be requested in those with a high- or intermediate-risk clinical syndrome. A positive result on a line blot or cell-based assay should be confirmed with an independent, tissue-based method.[5] False-positive results lead to incorrect diagnoses, divert efforts from making the right diagnosis and trigger unnecessary, serial screening for an underlying malignancy. An unexpected antibody result should not override clinical judgement.

Voltage-gated potassium channel (VGKC) antibodies have been a significant source of diagnostic confusion. VGKC antibodies that do not react with LGI1 or CASPR2 are not associated with distinct clinical syndromes and are common in healthy individuals. LGI1 and CASPR2 antibodies comprise only 15% of VGKC-positive results.[29]

In summary:

1 Paraneoplastic antibodies should usually only be requested in patients with a high pre-test probability of a paraneoplastic syndrome.
2 Whenever possible, both serum and CSF should be tested.
3 Antibodies against neuronal cell surface antigens detected in the serum but not in CSF should be reassessed in a reference laboratory.
4 A positive result on commercial line blots or cell-based assays should be confirmed with brain immunohistochemistry, especially if only serum has been tested, if the antibody titre is low, or the result is not concordant with the clinical syndrome or the type of cancer.
5 A positive result that is incongruent with the clinical phenotype and/or tumour should be treated with suspicion and, if possible, re-evaluated in a laboratory with special expertise in the evaluation of paraneoplastic antibodies (Table 3).

Screening for malignancy

The underlying malignancy may be undetectable at the time of presentation with a neurological paraneoplastic syndrome, but most tumours are found in the first 2 years after the onset of symptoms. When initial tumour screening is negative and the patient has a high-risk phenotype and either a high-risk antibody or an intermediate-risk antibody plus demographic features associated with increased risk of malignancy (e.g. older age, smoking history), screening investigations should be repeated every 4–6 months for the next 2 years.[6]

Table 3 Reference laboratories for anti-neuronal antibody testing

Australia
Pathology Queensland: Immunology Central Laboratory, Level 4, Block 7, Herston Hospital Campus, Herston Road, Herston, QLD 4029
kerri.prain@health.qld.gov.au
PathWest Laboratory, Level 3, PP Block, QE II Medical Centre, Nedlands, WA 6009
chris.bundell@health.wa.gov.au
Central Sydney Immunology Laboratory, NSW Health Pathology - East, Royal Prince Alfred Hospital, Missenden Road, Camperdown, NSW 2050
slhd-rpa-clinicalimmunology@health.nsw.gov.au
Westmead Hospital, Sydney
david.mcdonald2@health.nsw.gov.au
New Zealand
Department of Immunology/Serology, LabPLUS, Auckland City Hospital, Auckland
paul.austin@tewhatuora.govt.nz
Laboratories offering comprehensive anti-neuronal antibody testing and research studies
Mayo Clinic Laboratories
3050 Superior Drive NW, Rochester, MN 55905, United States of America
mckeon.andrew@mayo.edu
Neuroimmunology Laboratory, Hospital Clinic de Barcelona, Carrer Villarroel, 170, 08036, Barcelona, Spain
rruizg@clinic.cat (for routine testing)
jdalmau@clinic.cat (for special investigations)

Kelch-like protein 11 (KLHL11) antibody

New paraneoplastic antibodies continue to be discovered, but most of them have been found in, at most, a handful of patients, and the clinical and oncological correlations are still unclear. One new antibody that has been identified in a significant group of patients is the KLHL11 antibody. KLHL11 is an intracellular antigen involved in protein ubiquitination. The antibody is found in serum and CSF. It is a biomarker of a T-cell-mediated autoimmune response. The typical patient is an adult male presenting with subacute rhombencephalitis with ataxia, diplopia, dysarthria and often bilateral sensorineural hearing loss, tinnitus and vertigo.[30–32] There is a strong association with testicular germ cell tumours, but the neurological symptoms nearly always precede discovery of the tumour. MRI may be normal or show T2 hyperintensity and enhancement in the internal auditory canal, brainstem or cerebellum. The symptoms do not usually improve with immunotherapy or treatment of the tumour, and the long-term prognosis is poor. The KLHL11 antibody is not included in most commercial antibody panels.

Immune checkpoint inhibitors

Immune checkpoint inhibitors target proteins regulating the immune system and are effective in treating certain types of malignancy, but they can trigger immune-related adverse events including neurological paraneoplastic syndromes, which chiefly affect the central nervous system. Most of these paraneoplastic syndromes occur in the first 3–4 months of starting treatment. The clinical presentation, the type of cancer and anti-neuronal antibody closely resemble spontaneous paraneoplastic syndromes. Anti-neuronal antibodies have been detected in asymptomatic patients before they received an immune checkpoint inhibitor, this may predict increased risk of developing a paraneoplastic syndrome.[33]

Treatment

Treatment is based on expert opinion rather than evidence-based data. There are three general approaches: treatment of the tumour, suppression of the immune response and symptomatic treatment, for example, benzodiazepines for stiff person syndrome and amifampridine (3,4-diaminopyridine) for Lambert Eaton myasthenic syndrome. Details of recommended treatments can be found elsewhere.[21] Paraneoplastic syndromes associated with antibodies against intracellular antigens seldom improve, but when an antibody against a cell surface antigen is involved, treatment is often very beneficial.

Conclusions

Neurological paraneoplastic syndromes are immune-mediated disorders. They can affect any part of the nervous system. Identical clinical and pathological manifestations can occur in the absence of malignancy. Anti-neuronal antibodies directed against intracellular antigens are not involved in the pathogenesis of the neurological disorder, but when used judiciously, they are useful biomarkers of paraneoplastic syndromes and often provide clues to the site of an occult malignancy. Antibodies directed against neuronal cell surface antigens are not only useful biomarkers but also are involved in the pathogenesis of the neurological disorder.

Data availability statement

Data sharing is not applicable to this article as no datasets were generated or analysed during the current study.

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