Paraneoplastic encephalitis: clinically based approach on diagnosis and management

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ABSTRACT

Paraneoplastic neurological syndromes (PNSs) comprise a subset of immune-mediated nervous system diseases triggered by an underlying malignancy. Each syndrome usually shows a distinct clinical presentation and outcome according to the associated neural antibodies. PNSs generally have a subacute onset with rapid progression and severe neurological disability. However, some patients may have hyperacute onset or even show chronic progression mimicking neurodegenerative diseases. Updated diagnostic criteria for PNS have been recently established in order to increase diagnostic specificity and to encourage standardisation of research initiatives related to PNS. Treatment for PNS includes oncological therapy and immunomodulation to halt neurological deterioration although current treatment options are seldom effective in reversing disability. Nevertheless, growing knowledge and better understanding of PNS pathogenesis promise better recognition, earlier diagnosis and novel treatment strategies. Considering that PNSs provide a model of effective anticancer immunity, the impact of these studies will extend far beyond the field of neurology.

INTRODUCTION

Paraneoplastic neurological syndromes (PNSs) are a heterogeneous group of immune-mediated diseases related to cancer that are not directly caused by the tumour; instead, an immune reaction initiated within the tumour subsequently leads to neuronal destruction or functional blockade.[1] Both the peripheral and central nervous system (CNS) can be affected, the latter being more frequently involved.[2] When there is a clearly established relationship between cancer and the immune mediated effects affecting the cerebral hemispheres, the term paraneoplastic encephalitis (PE) may be used. In contrast, immune-mediated disorders affecting other CNS structures, such as the cerebellum, or the spinal cord can be termed as cerebellar syndrome and myelopathy, accordingly. Over the past decade, expanding knowledge on the pathogenesis and clinical features along with improved diagnostic tools allowed an easier recognition of PE. Current guidelines propose clear-cut, recognisable clinical phenotypes associated with PE. Importantly, demonstration of the immunological relationship between the clinical phenotype and the underlying malignancy is necessary for antibody-guided tumour screening and early management.[3] Finally, the growing use of cancer immunotherapies impose new challenges on PE diagnosis and management in clinical scenarios previously not encountered by physicians and medical researchers.[4 5]

Here, we aim to provide an updated overview of the pathogenesis, diagnosis and management of PE and other paraneoplastic disorders of the CNS.

GENERAL EPIDEMIOLOGICAL ASPECTS OF AUTOIMMUNE ENCEPHALITIS IN COMPARISON TO PE

The incidence of autoimmune encephalitis (AE) has risen over the past decades due to the discovery of several novel neuronal antibodies (Abs) used as diagnostic biomarkers, an increased awareness among neurologists and other physicians, and the development of commercial assays to detect the aforementioned Abs in all clinical settings.[6] A recent nationwide study in France estimated the incidence of AE to be approximately 2 per million person-years.[6] Interestingly, a predominance among African-American ancestry has also been proposed.[7] Moreover, diverse demographic specificities have been described according to the associated antibody; for example, one of the the most common AE, anti-N-methyl D-aspartate receptor (NMDAR) encephalitis, shows a female predominance between 12 and 45 years, whereas leucine-rich glioma-inactivated protein 1 (LGI1) and contactin associated protein 2 (CASPR2) are more frequently diagnosed in elderly men.[8 9]

In contrast, PE is even far less frequent, with an estimated incidence between 0.2/100 000 and 0.8/100 000 person-years, and an expected prevalence of 5.4/100 000 person-years, predominantly in the 6th and 7th decade of life.[6 10–12] Concurrently, the incidence has also risen from the initial estimation of 1 in every 10 000 patients with cancer to population-based data of 1 in every 300 patients.[6 11 13] Furthermore, its incidence is expected to continue increasing due to the growing use of immune checkpoint inhibitors (ICIs) for cancer immunotherapy in an expanding spectrum of oncological indications.[4 5 14 15]

ROLE OF CANCER IN THE IMMUNE TOLERANCE BREAKDOWN

PNSs are considered to be driven by an immune cross-reaction between tumourous and neural antigens. The exact underlying mechanisms leading to immune tolerance breakdown are still elusive.

Nevertheless, recent studies have unravelled key elements that may explain immune tolerance loss in some PNS.[16]

The tumourous microenvironment and protein expression are considered to play a major role in the pathogenesis, since tumours of patients with PNS have been found to express abnormal neuronal antigens that are recognised by the immune system, supporting the cross-reactive immune response hypothesis. For instance, ovarian teratomas from patients with NMDAR encephalitis have been found to contain neural tissue and more frequently express the GluN1 subunit compared with control teratomas.[17] This in turn may lead to rapid infiltration of the tumourous tissue with immune cells unleashing a cross-reaction between the tumour and the CNS.[17] Similarly, ovarian cancers from patients with paraneoplastic cerebellar ataxia and Yo-Abs have been shown to harbour several genetic alterations in the genes encoding CDR2L and CDR2, the antigens of Yo-Abs.[18] Moreover, T-cell infiltrates are more abundant in ovarian tumours associated with anti-Yo cerebellar ataxia.[18] This T-cell-mediated pathogenesis in anti-Yo cerebellar ataxia is also supported by transcriptomic studies.[19] Altogether, these data suggest that tumourous cells abnormally expressing neural proteins may enhance the antitumour immune response, and trigger a cross-reaction against the CNS.

However, the mechanisms of the immune breakdown in PNS probably varies according to the associated antibody or cancer. For example, breast cancer associated with anti-Yo cerebellar ataxia does not overexpress CDRL2 (as occurred in ovarian malignancies) but human epidermal growth factor-2 (HER2).[20] However, overexpression of HER2 does not seem to play a major role in cerebellar ataxia with Ri-Abs related to breast tumours.[20] Moreover, even though all small cell lung cancers (SCLC) highly express the HuD antigen, the main protein recognised by Hu-Abs,[21] no HuD mutations have so far been identified in the tumour of patients with Hu-Abs, and only a small fraction of patients with SCLC develop PNS.[22] Furthermore, Hodgkin's lymphomas of patients with Abs targeting the Delta/notch-like epidermal growth factor-related receptor (DNER) and rapidly progressive cerebellar syndrome (RPCS) have not been found to express DNER.[23] Therefore, other factors may play a role in the development of PNS, such as the exposure to certain micro-organisms, or other immune boosters including the treatment with Bacillus Calmette–Guérin or ICI.[24 25] In this regard, several mechanisms of action have been proposed to explain the wide spectrum of neurological immune-related adverse events (n-irAEs) secondary to ICI use.[26] However, a PNS-like pathogenesis is supported by an animal model for a subset of these toxicities.[27] The proposed mechanisms for formation of PNS are summarised in figure 1.

Besides these recent advances in the field, the precise pathogenesis of PNS largely remains terra incognita and further work is necessary to understand the mechanisms leading to the immune activation in these patients. Comprehensive studies of the patients' tumours are warranted, including genetic and histological characterisation. Furthermore, while several associations between non-paraneoplastic AE and certain human leucocyte antigen (HLA) alleles have already been described,[28–31] the presence of a genetic predisposition to PNS remains to be clearly defined.[32]

UPDATED DIAGNOSTIC CRITERIA FOR PNS

The first clinically applicable criteria for the diagnosis of PNS were published in 2004, and defined a 'definite PNS' by the presence of a 'classical' neurological syndrome with concomitant cancer regardless of antibody status or cancer type.[33] In addition, the presence of a neurological syndrome without cancer but with 'onconeural Abs' allowed to make a definite PNS diagnosis. Thus, the diagnosis principally relied on the mere presence of a cancer
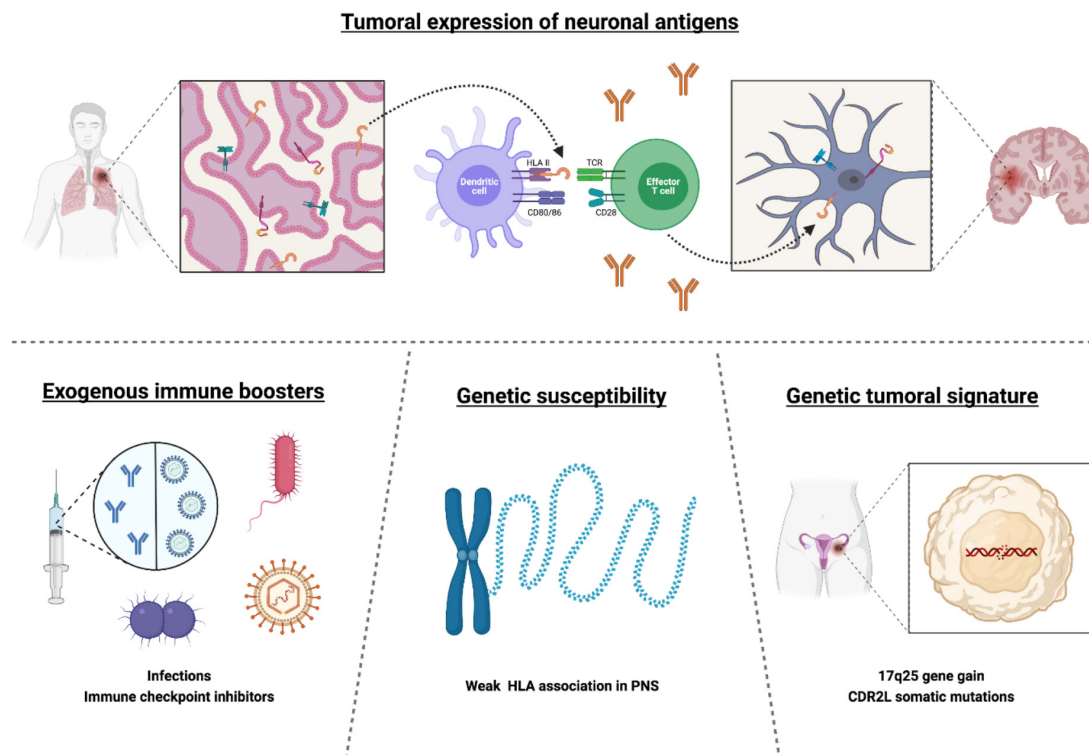

Figure 1 Proposed mechanisms in paraneoplastic encephalitis. HLA, human leucocyte antigen; PNS, paraneoplastic neurological syndromes; TCR, T cell receptor.
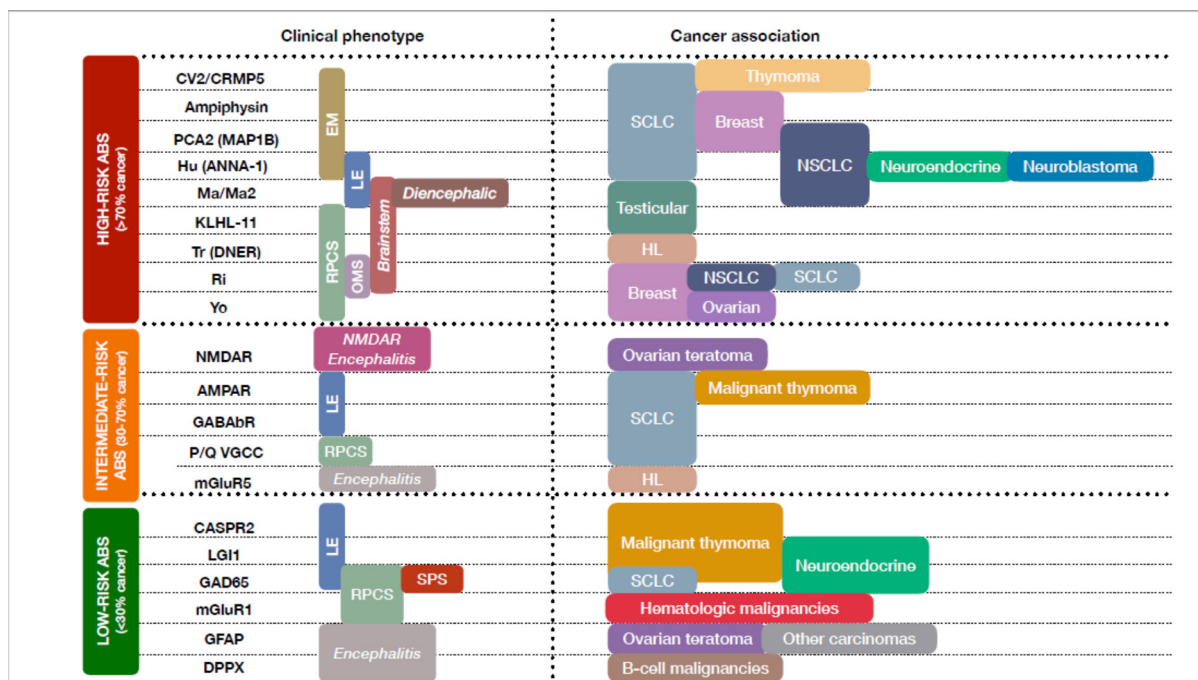
Figure 2 Main clinical phenotype and associated cancer in paraneoplastic encephalitis. Abs, antibodies; ANNA, antineuronal nuclear antibody; AMPAR, α-amino-3-hydroxy-5-methyl-4- isoxazolepropionic acid receptor; CRMP5, collapsin response-mediator protein 5; CASPR2, contactin-associated proteinlike 2; DPPX, dipeptidyl peptidase-like protein; DNER, delta/notch-like epidermal growth factor-related receptor; EM, encephalomyelitis; GABAaR, gamma-aminobutyricacid- A receptor; GABAbR, gamma-aminobutyric acid-b receptor; GAD, glutamic acid decarboxylase; GFAP, glial fibrillar acidic protein; HL, Hodgkin lymphoma; KCTD16, potassium channel tetramerisation domain containing; KLHL11, Kelch like protein 11; LGI1, leucine rich gliomainactivated protein 1; LE, limbic encephalitis; MAP1B, microtubule-associated protein 1B; mGluR1, metabotropic glutamate receptor type 1; mGluR5, metabotropic glutamate receptor type 5; NMDAR, n-methyl-aspartate receptor; NSCLC, non-small cell lung cancer; OMS, opsoclonus-myoclonus syndrome; PCA, Purkinje cell antibody; RPCS, rapidly progressive cerebellar syndrome; SCLC, small cell lung cancer; SPS, Stiff Person Syndrome; VGCC, voltagegated calcium channel.

or onconeural Ab, without recognising the relevance of the association between them and the clinical phenotype. Recently, an updated criteria for PNS diagnosis has been proposed in order to amend this major point, allowing therefore to establish more accurate causal relationships between cancer and PNS.[3]

The current criteria for PNS diagnosis propose a three level-based approach relying on clinical phenotype, antibody status and cancer association. Both clinical presentations and neural Abs are classified as high, intermediate, or low risk, mainly according to their epidemiological probability of associating an underlying malignancy (figure 2). Overall, the tumours most frequently related to PNS are SCLC, non-SCLC (NSCLC), breast cancer, gynaecological malignancies (including ovarian teratomas), lymphomas, neuroendocrine tumours and malignant thymomas. Notably, the occurrence of a concordant clinical phenotype and antibody with a rare cancer should always prompt the exclusion of another more commonly related malignancy.[3]

Each of the aforementioned levels can be quantified using the 'PNS-Care score' to allow for the diagnosis of PNS on four levels of certainty: definite, probable, possible or non-PNS. 'Definite' PNS corresponds to an underlying malignancy that has strong epidemiological associations with either high-risk or intermediate-risk Abs and high-risk or intermediate-risk phenotypes. In other words, the current criteria propose that PNS can be diagnosed with highest level of certainty only in cases where the corresponding cancer is identified given the current pathophysiological understanding of these syndromes. In contrast, cases where no cancer is identified, 'probable' or 'possible' PNS may only be diagnosed regardless of Abs or clinical phenotype.

It is still valuable to define 'probable' or 'possible' PNS since a more rigorous cancer screening and follow-up is warranted in these cases.[3] The 'PNS-Care score' and the association of Ab, phenotype and cancer levels are displayed in figure 2.

In summary, the updated criteria provide a homogeneous approach for PNS classification, which in turn enables for more accurate diagnoses, as well as valuable and reproductible research. The possible drawback of the revised criteria is the relatively low sensitivity in cancers rarely linked to PNS in epidemiological studies, or in which less clinical and immunopathological experience was accumulated but, at the same time, this prevents spurious and non-meaningful associations from being reported.

MAIN CLINICAL PRESENTATIONS OF PE

The clinical presentation of PE is diverse and dependent on the associated antibody (figure 2).[3] The main clinical syndromes along with their relevant paraclinical associations, are discussed in the following paragraphs.

Limbic encephalitis (LE) is characterised by a subacute onset of confusion, psychiatric symptoms and/or short-term memory deficits progressing over less than 3 months, coupled with bilateral medial-temporal hyperintensities on MRI, and either cerebrospinal fluid (CSF) inflammatory changes or pathological electroencephalography (EEG) suggesting new-onset temporal lobe epilepsy; alternative causes of LE or involvement, such as herpes simplex encephalitis or gliomas, should always be ruled out.[34] High-risk Abs most commonly associated with LE are Hu and Ma2, although their clinical involvement often exceeds the

limbic system.[35–37] Intermediate-risk Abs frequently encountered include gamma-aminobutyric acid, receptor (GABAbR) and α-amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid receptor (AMPAR).[38–40] For the former, an associated cancer is almost universally present when concomitant potassium channel tetramerisation domain-containing 16 (KCTD-16) Abs are identified.[41 42] The most frequently encountered cancers are SCLC for Hu, GABAbR and AMPAR-Abs, testicular malignancies for Ma2-Abs in young males and NSCLC in the elderly. However, based only on clinical grounds, it may be challenging to distinguish paraneoplastic from non-paraneoplastic cases, therefore, antibody detection is of utmost importance to guide through adequate cancer screening.[3]

RPCS is defined as a subacute-onset cerebellar ataxia that often progresses over weeks to months to severe disability. Vermis involvement, which manifests as gait and truncal ataxia, usually predominates over cerebellar hemispheric signs (limb ataxia or dysmetria). Besides, there is generally no evidence of structural cerebellar pathology on neuroimaging in the acute phase.[43] Ocular manifestations include horizontal or downbeat nystagmus, diplopia and oscillopsia in the majority of affected individuals.[44] The most common Abs associated with paraneoplastic RPCS is Yo-Abs, which almost universally appear in women with ovarian or breast cancer.[43] Another Ab typically associated with RPCS is DNER-Abs, found in younger males with Hodgkin's lymphoma.[23] In contrast to the more typical presentations of patients with Yo- and DNER-Abs, brainstem-cerebellar syndrome with Ri-Abs can manifest with a slowly progressive course mimicking neurodegenerative diseases such as progressive supranuclear palsy.[45] Moreover, hyperacute presentations mimicking cerebrovascular disease have also been described in some exceptional cases of paraneoplastic RPCS.[46]

Brainstem encephalitis may include cranial nerve abnormalities, bulbar syndrome, gait or limb ataxia, pyramidal signs and autonomic instability. Isolated brainstem manifestations are uncommon, but may be seen with Ma2 and Hu-Abs.[37 47] For the former, concomitant involvement of limbic system is the classic presentation. Moreover, co-occurring diencephalic involvement is also typical of anti-Ma2 PE, and includes hyperphagia, hyperthermia, hypersomnolence and new-onset endocrinopathy such as diabetes insipidus.[37] Interestingly, sensorineural hearing loss with other signs of brainstem involvement might be suggestive for PNS with Kelch-like protein 11 (KLHL-11) Abs.[48 49]

Encephaloneuromyelitis is defined as a combination of multiple involvement of the central and peripheral nervous system.[33] Sensory neuronopathy and LE are the most common clinical presentations of the peripheral and CNS, respectively.[2 11] These complex and variegated phenotypes are frequently observed in patients with high-risk antibodies, such as Hu, CV2/CRMP5 and amphiphysin.[36 50]

Opsoclonus-myoclonus (OMS) is characterised by chaotic, high velocity, high amplitude, involuntary ocular movements without intersaccadic intervals. Myoclonus is also a non-rhythmic, action type movement disorder affecting the limbs, trunk or head. Two main different categories of OMS have been described: paraneoplastic and idiopathic, the latter being probably immune-mediated.[25 45] Isolated OMS associated with Ri-Abs is found more frequently in women with breast malignancies.[25] Moreover, OMS corresponding to severe cerebellar dysfunction may be encountered in RPCS syndromes associated with Yo and Ma2-Abs, although not frequently.[37 43]

DIAGNOSTIC WORKUP AND DIFFERENTIAL DIAGNOSIS
In the presence of a patient with suspected encephalitis, based on the development of psychiatric symptoms, cognitive deficits or altered mental status, a comprehensive ancillary evaluation should promptly be performed to rule out infectious, vascular and toxic-metabolic causes (table 1). After exclusion of the aforementioned aetiologies, certain cases with objective proof

Table 1 Common differential diagnoses of paraneoplastic encephalitis

Common aetiologies in differential diagnosis of PNS	Key differences
Vascular	*MRI features/cardiovascular risk factors present*
Percheron artery occlusion	Bilateral thalamic T2 FLAIR hyperintensities with diffusion restriction
Infectious	*MRI features*
HSV-1	T2 hyperintense signal on MRI with presence of haemorrhagic necrosis of the affected area
VZV	Cerebellar oedema
HHV-6	Bilateral hyper intensity of hippocampus regions
Whipple disease	Bilateral hyper intensity of hippocampus regions
Listeria meningitis	Contrast enhancing ring lesions in the brainstem
Tuberculous meningitis	Diffuse basal enhancement with enhancing exudates, hydrocephalus
Creutzfeld-Jakob disease	DWI basal ganglia or cortical hyperintensities
Neurosyphilis	Unilateral/bilateral mesiotemporal FLAIR hyperintensities on MRI. Exclusion with specific testing for syphylis
Toxic-metabolic	
Uraemic encephalopathy	Serum metabolic profile and history are suggestive
Hepatic encephalopathy	*MRI features*
Septic encephalopathy	Normal or not specific
Wernicke-Korsakoff encephalopathy	Normal or not specific
Cancer and cancer therapy related	Wide range of findings from cortical-subcortical haemorrhages, ischaemia, to oedema of the basal ganglia
Primary CNS tumours	Normal to hyperintense FLAIR fo mammillary bodies
New CNS metastasis or known metastatic progression or leptomeningeal carcinomatosis	*MRI features*
Complications of cranial radiation therapy (SMART syndrome)	Exclusion with MRI
Chemotherapy-related encephalopathy	Exclusion with MRI
	Contrast enhancement of the leptomeninges on MRI
	Reversible FLAIR cortical hyperintensities with contrast enhancement
	Various findings depending on the chemotherapeutic agent used and type of encephalopathy

CNS, central nervous system; HHV-6, human herpes virus-6; HSV-1, herpes simplex virus-1; PNS, paraneoplastic neurological syndromes; SMART, stroke-like migraine attacks after radiation therapy; VZV, varicella zoster virus.
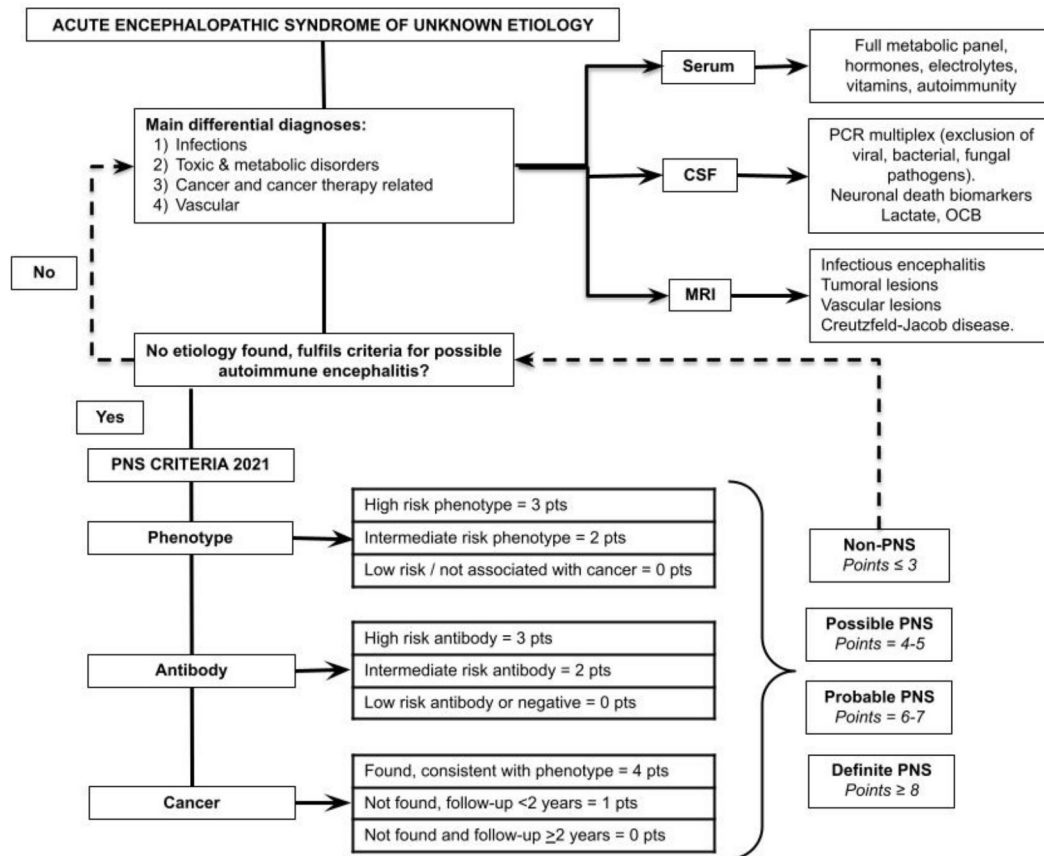
Figure 3 Clinical approach to diagnose paraneoplastic encephalitis. CSF, cerebrospinal fluid; OCB, oligoclonal bands; PNS, paraneoplastic neurological syndrome.

of neuro-inflammation are highly suggestive of an autoimmune CNS disorder.[51 52] Hence, it is important to search for inflammatory patterns on neuroimaging which might in turn support the diagnosis, such as T2 FLAIR abnormalities involving the brainstem, limbic or extralimbic regions on MRI.[35–37 48 53–55] Rarer presentations may include cortical or leptomeningeal enhancement or demyelination patterns.[56] However, up to 50% of patients with AE may have a normal MRI.[57 58] In these cases, positron emission tomography (PET) may reveal signs suggestive of AE, presumably earlier than MRI.[59] Conversely, EEG findings are typically nonspecific (with rare exceptions such as the 'extreme delta brush' pattern typical of anti-NMDAR encephalitis) and may reveal generalised or focal slowing, and focal (usually temporal) epileptiform discharges.[60] Finally, EEG and MRI findings back up with CSF studies revealing either lymphocytic pleocytosis, elevated protein levels, or oligoclonal bands, alone or in combination, in up to 70%–80% of cases are highly suggestive of an autoimmune CNS disease.[23 35–37 39 43] An algorithm to approach the diagnosis of PNS is summarised in figure 3.

CONSIDERATIONS FOR NEURONAL ANTIBODY TESTING
The identification of neural Abs is essential for the diagnosis of PNS. Nevertheless, their detection is challenging since standardised techniques are limited. Generally, Abs against neuronal surface antigens are detected in most clinical settings with commercially available cell-based assays (CBAs) transfected to express NMDAR, LGI1, CASPR2, AMPAR, GABAbR and dipeptidyl-peptidase-like protein 6. However, its sensitivity may be dependent on the sample used for antibody detection

in certain cases.[61] For example, false negative results may be obtained for Abs against AMPAR, GABAbR and LGI1, especially when using CSF specimens.[61] On the contrary, false positive results for NMDAR Abs are more frequently observed when serum is tested compared with CSF.[62] The main limitation of the use of this commercial panel is the missing recognition of Abs other than the aforementioned ones.

On the other hand, high-risk antibodies targeting intracellular antigens are often detected using commercially available immunodots.[63 64] Despite their undeniable advantages (they are easy to run, not requiring specially trained personnel, and quickly provide results), this method has shown a high rate of false positive results, mainly for the detection of Yo-Abs,[65 66] probably because only CDR2 is used as antigen in these dots and not CDR2L. Moreover, the discordance between the identified Ab and the clinical phenotype should always raise concerns of a false positive result, that is, Yo-Abs in a man with no cancer or with a low-risk phenotype.[65] Still, inconclusive results may arise, and if a negative result is obtained despite a high clinical suspicion, samples should be referred to research expert laboratories for additional testing.[3]

For these limitations, other tests with higher sensitivity and specificity are used in most research laboratories such as western-blotting using rat brain proteins and/or recombinant proteins. Murine tissue-based immunohistochemistry or immunofluorescence with serum or CSF is also used to identify the presence of non-specific IgG antibodies targeting neural antigens. If a specific staining reaction is observed, more specific tests such as in-house CBAs using human embryonal kidney 293 cells expressing the antigen of interest are used to confirm the presence of a specific

neuronal Ab.[67] Although this approach is considered to be the gold standard, it is mainly limited by its technical complexity and a need of highly trained personnel. However, commercially available tissue-based assays are now available and have shown to increase diagnostic yield in comparison to CBA alone.[68] [69] Western-blotting with recombinant proteins is a gold-standard method to confirm the presence of certain high-risk Abs.[70]

Altogether, these data support the recommendation of using different methods for Ab detection, as well as the importance of always considering the results in their clinical context and confirming doubtful or discordant results in reference laboratories.

TREATMENT

The management of patients with PE is complex and often require multidisciplinary discussion. First, treatment of the underlying malignancy is essential, as it would theoretically suppress the exposure to the tumour antigens that initially triggered the immune reaction.[3] Therefore, a prompt diagnosis of an underlying tumour allowing earlier tumour treatment is of utmost importance. Tumour screening should ideally be guided by the clinical phenotype and, especially, by the associated antibody.[3] When no particular tumour is suspected or antibody status is not known yet, a good general approach is performing a full-body CT followed, if negative, by fluorodeoxyglucose-PET/CT. However, cancer identification is often a difficult task in PNS patients, since tumour is frequently of small size or it is even limited to a little metastatic lymph node.[71] In these cases, Ab-guided selective cancer screening may warrant extensive ancillary testing with surgical exploration. For example, SCLC in patients with Hu-Abs is frequently limited to few mediastinal lymph node metastasis of less than 2 cm in diameter without visible lung mass, diagnosis being therefore only possible through mediastinoscopy and biopsy.[36] Similarly, ovarian cancer in patients with Yo-Abs may not be identified by pelvic CT/MRI and PET-scan; thus, in a compatible clinical scenario, surgical exploration of the pelvic organs may be warranted if imaging is inconclusive.[43] Likewise, orchiectomy is recommended in young men with testicular microcalcifications and confirmed Ma2 antibodies with compatible clinical presentation.[3] In addition, burn out testicular tumours are also frequent in patients with KLHL-11 Abs and the diagnosis is commonly established on abdominal lymph node metastasis on PET/CT.[49]

Second, the early administration of immunotherapy has shown to be of utmost importance to improve long-term outcomes in patients with AE.[9] [72] Therefore, immunomodulatory treatments should be started as soon as criteria for possible AE are met, and other alternative causes have been excluded.[34] However, there is no solid evidence supporting the superiority of one agent over another and current strategies are supported mostly by the findings of previous observational retrospective studies.[5] [34] [45]

The most developed immunotherapeutic strategy for PNS is based on a two-step approach. First-line agents include high-dose corticosteroids, intravenous immunoglobulin (IVIG) and plasma exchange (PLEX), administered individually or in combination.[73] High-dose methylprednisolone and IVIG are the most commonly chosen first-line agents due to their availability, cost-effectiveness and relatively good safety profile. Conversely, PLEX is frequently postponed due to its low availability and tolerability.[74] For refractory cases, second-line treatments using cyclophosphamide (CP) and/or rituximab (RTX) should be considered. While CP is an alkylating agent acting by inhibition of B and T cells, RTX is a monoclonal antibody specifically directed to B cell lineage.[74] However, the broad spectrum of immune cells depleted by these therapies may lead to undesirable side effects including secondary infections, higher risk of developing other malignancies or even the potential reduction of antitumour immunity.[75]

As for emerging ICI-related complications, the treatment of n-irAEs meeting PNS criteria should not differ from the management of classic PNS, except for the withdrawal of the ICI-therapy.[76] Given the lack of oncological treatment alternatives for these patients, rechallenge with ICI can be considered in some specific n-irAEs scenarios.[77] [78] However, in the setting of PNS, reported cases of worsening and fatal outcome discourage this proposition,[79] but future research is warranted in this topic.

Due to the aforementioned potentially serious side effects of the current immunotherapies, the development of novel therapies targeting specific immune pathways involved in the pathogenesis of PNS is critical. In this regard, natalizumab and tacrolimus have been explored in cases of PNS with mainly with Yo-Abs and Hu-Abs,[80] [81] while bortezomib, tocilizumab and intrathecal methotrexate have been explored in refractory cases with Abs against cell surface antigens.[82–86] Unfortunately, data are limited to small case series, therefore, further studies are needed to validate their value in the treatment of PNS.

CONCLUSIONS AND FUTURE PERSPECTIVES

PE comprises a small subset of autoimmune disorders associated with a growing number of neuronal Abs and a heterogeneous pathophysiology. Despite major advances in the knowledge of PNS pathogenesis and the recent update of their diagnostic criteria, a deeper understanding is still required to promote their diagnosis and optimal management. The development of novel targeted therapies is crucial to improve PNS outcomes while preserving the beneficial antitumour immunity. Furthermore, given the rarity of these diseases, international collaborations are essential to better characterise large cohorts of patients and to design prospective studies on the management and outcome of PNS.

Main messages

⇒ The updated criteria for paraneoplastic neurological syndromes help to standardise the clinical approach towards diagnosis.
⇒ Specific knowledge of the caveats of commercial antibody testing methods is required to avoid under/overdiagnosis of these syndromes.
⇒ Early tumour detection, removal and concomitant immunomodulation are necessary to ensure better outcomes.

Current research questions

⇒ Is a unified pathogenesis model for paraneoplastic neurological syndromes and encephalitis possible?
⇒ Can we identify molecular mechanisms for specific targeted therapy to ensure better outcomes?
⇒ Can we develop disease specific targeted therapies without affecting antitumour immunity to ensure better outcomes?

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Self assesment questions

1. Paraneoplastic neurological syndromes have subacute onset and progress to major disability.
2. Pathogenesis of paraneoplastic neurological syndromes is heterogeneous.
3. Updated criteria for paraneoplastic neurological syndromes does not require antibody status to establish the diagnosis.
4. In cases of discordant findings between antibodies found and clinical phenotype, antibody results are superior.
5. Tumour identification in paraneoplastic neurological syndromes can be challenging;

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Answers

1. True
2. True
3. False
4. False;
5. True