Binks et al 2021 Paraneoplastic neurological syndromes: a practical approach to diagnosis and managament

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Abstract

Paraneoplastic neurological syndromes (PNS) are the immune-mediated effects of a remote cancer. Overall, PNS affect ~ 1:300 patients with a cancer and are characterised by an autoantibody response against antigens expressed by the tumour. Classically, well-characterised 'onconeuronal' antibodies target intracellular antigens and, hence, do not gain access to their antigens across intact cell membranes. Here, the pathogenic mediators are likely to be neuronal-specific T cells, and this immune response is variably sensitive to immunotherapies and often helps direct the search for a specific set of tumours. By contrast, many newly-emerging autoantibodies exhibit oncological associations but target cell surface epitopes. These autoantibodies likely exert direct pathogenic effects which lead to neurological symptoms that can involve both the central and peripheral nervous systems, and many of these patients show clear responses to immunotherapies. Overall, the coherence of the clinical, serological and oncological features in individual patients helps to determine their clinical relevance and hence guide management. In this review we summarise current knowledge and a practical approach to the investigation, diagnosis, treatment and outcomes of patients with suspected PNS.

Introduction

Paraneoplastic neurological syndromes (PNS) describe the remote neurological immune-mediated consequences of a systemic cancer. They affect ~ 1:300 patients with tumours, yet population level epidemiology suggests an incidence rate of only between ~1-8/100,000 person-years,[1,2] indicating an ongoing under-recognition. Distinctive clinical and serological features (**Tables 1-3**) typically direct the search for a tumour, which occurs prior to tumour detection in around 65% of PNS. In rare cases, this tumour may only emerge months or years after the neurological syndrome, demanding ongoing clinical vigilance.[1,3] A key feature of PNS is that the cancer triggers the immune response and so, it should express the autoantigen to which the immune response (including an autoantibody) is directed: this ensures a direct biological link between the cancer and PNS.

Expert guidelines in 2021 have redefined aspects of these disorders in light of the description of novel antibodies and the most robust emergent clinical-serological-oncological associations.[4] Amongst other benefits, these observed relationships avoid the spurious attribution of common cancers to neurological presentations with an alternative explanation, and hence encourage accurate diagnosis and prognostication. In this classification, clinical presentations and associated autoantibodies may be broadly defined as 'high' or 'intermediate' risk for paraneoplastic aetiology (**Box 1**).[4,5] High risk clinical presentations are reflected by epidemiological studies which consistently identify autoantibody patterns with subacute cerebellar degeneration, encephalomyelitis, limbic encephalitis and sensory neuronopathy as the leading PNS in European cohorts.[1–3] The intermediate risk groups show recognised, but less reliable, clinical-serological associations.

Box 1: Classic Paraneoplastic Presentations[4,5]

A: High risk, frequently associated with tumours

Central Nervous System

Encephalomyelitis

Limbic Encephalitis

Subacute Cerebellar Degeneration

Opsoclonus Myoclonus

Peripheral Nervous System and Neuromuscular junction / muscle

Subacute sensory neuronopathy

Chronic gastric pseudo-obstruction

Lambert-Eaton Myasthenic Syndrome

Dermatomyositis

B: Intermediate risk, frequently associated with tumours

Central Nervous System

Encephalitis

Brainstem encephalitis

Isolated myelopathy

Peripheral Nervous System and Neuromuscular junction / muscle

Polyradiculopathy

Stiff person syndrome

Myasthenia gravis

Paraneoplastic antibodies in context

Traditionally, paraneoplastic syndromes have been associated with 'well-defined onconeuronal' antibodies, which almost always target intracellular proteins and hence show limited direct pathogenic significance. Nevertheless, their presence often indicates a robust (nearly 100% in some cases) link with a tumour in addition to distinct clinical associations (**Table 1**), for example Yo-antibodies and cerebellar degeneration.[6] Such associations clinically guide cancer identification and can expedite and focus treatments.

More recently, an explosion of scientific discovery in the field of cell-surface directed neuroglial antibodies, which show clear pathogenic potential, has yielded several further clinical-serological associations. However, the frequencies of cancer associated with these newer autoantibodies varies according the antigenic target, and the age and sex of the patients. Examples include N-methyl-D-aspartate receptor (NMDAR)- autoantibodies and ovarian teratomas,[7] which are observed in young women but very rarely in young children or men; α-amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid (AMPA)-receptor antibodies

which are associated with ~50% rate of cancers, especially small cell lung carcinoma (SCLC), but mainly in the older patients;[8] and γ-aminobutyric acid $(GABA)_B$ receptor autoantibodies which associate with a ~50% rate of SCLC, only in patients over 50 years of age (**Table 1**).[9] Also, some surface neuroglial antibodies are associated with very low rates of cancer.[10]

By contrast to intracellular-directed antibodies, those targeting cell-surface proteins - which have access to their native targets in the blood / CSF - are considered directly pathogenic as they bind *in vivo* and can trigger deleterious effects including complement fixation, receptor internalisation and direct modification to the function of their target proteins.[11,12] These causative antibodies will be detailed in our sister review (Uy, Binks and Irani, Practical Neurology, *in revisions*). Also, herein, we will not focus on autoantibodies in inflammatory myopathies, which have recently been reviewed in this journal [13], or the potential triggering of PNS after checkpoint inhibitor drugs,[14] as these likely show different underlying mechanisms to traditional PNS.[15] Myasthenia gravis may be associated with an underlying tumour, typically a thymoma, but is not further considered herein due to its absence from the updated 2021 guidelines.[4]

Pathophysiology

Role of onconeuronal antibodies

The exact role of intracellular antibodies remains unresolved, but they are unlikely to be direct mediators of disease. Although uptake and pathological effects of Hu-antibodies by Purkinje cells has been shown *in vitro*,[16] their infusion into various *in vivo* models does not consistently replicate disease despite achieving high antibody titres in the experimental animals.[17] Experiments with Ma2-antibodies yielded similar negative results.[18] However, some antibodies classically denoted as 'onconeuronal' do recognise extracellular domains of neuroglial proteins and thus could have a direct role in causation: for example, Tr-antibodies are closely associated with Hodgkin lymphoma and have been recognised to target the extracellular portion of the delta and notch-like epidermal growth factor-related receptor (DNER).[19]

The relatively high rate of many of these antibodies in patients with tumours but no accompanying neurological syndrome, for example, ~16% of SCLC patients with Hu-

antibodies [20] or Zic4-antibodies [21], and the frequent co-occurrence of more than one paraneoplastic antibody in an individual,[3] cautions against interpretation of the antibody result in isolation and may also suggest that the polyclonal immune response protects against tumour growth. Indeed, some investigators have proposed tumours to be more indolent in patients with a PNS.[22]

The likely origin of immunisation is the tumour itself, given immunohistochemical evidence of relevant antigen expression in cancers including SCLC[23], testicular seminoma [24] and ovarian carcinoma.[25] The accompanying peripheral immune response may translocate to the CNS in some patients. Overall, CSF studies point to intrathecal synthesis of antibodies [6,21,24] in CNS-predominant syndromes (versus absent intrathecal synthesis in those with PNS-only involvement).[26] This suggests an influx of lymphocytes to the CSF is key for triggering CNS syndromes, a finding which aligns with clonal $CD8^+$ T-cells and restricted T-cell receptor repertoires in post-mortem brain pathology.[27] It is likely that these cell types are the key disease effectors.

Genetic contributions

Major histocompatibility complex (MHC) molecules are essential to antigen presentation, T cell actuvation and autoantibody generation. Early – albeit limited - immunohistochemical observations suggested that tumours of patients with Hu-antibody PNS might have increased expression of MHC proteins, when compared to tumours in patients without autoantibodies.[28] More recently, it was demonstrated that Hu-antibody patients with PNS were significantly more likely to carry the Class II molecules HLA-DQ2 and HLA-DR3 than ethnically matched healthy controls.[29] By contrast, with Yo-antibodies, a risk haplotype DQA1*01:03-DQB1*06:03-DRB1*13:01 was reported as tumour-specific and observed mainly in patients with ovarian but not breast cancer, whereas a protective effect of DRB1*04:01 is observed across all patients.[30]

A different genetic predisposition has been suggested by somatic mutations in antigenic proteins. Taking Yo-antibody cerebellar degeneration, it has been shown that associated ovarian tumours, but not those found in patients without Yo-antibodies, expressed numerous genetic lesions in the antigenic CDRL2 (cerebellar degeneration-related protein 2-like, or Yo)

protein. It is plausible that these create neoantigens which drive the disease.[25] A differing mechanism has been elucidated in patients harbouring NMDAR-autoantibodies and ovarian teratoma. Explants of these – usually benign - tumours, and dissociated intra-teratoma B cells, were able to secrete NMDAR-autoantibodies *in vitro*. Furthermore, tumour immunohistochemistry revealed germinal-centre like structures housing T-cells, B-cells and the NR1 subunit – the key autoantibody epitope.[31] In this scenario, the tumours may act as ectopic lymphoid organs and initiate the directly pathogenic autoantibody response. Taken together, these early observations support a local tumour response, facilitated by genetic and other as-yet confirmed factors in at-risk patients, which gains traction in the CNS with either autoantibodies or cytotoxic T-cells as the key pathogenic effector. Future efforts to systematically map steps along this pathogenic pathway will offer clearer insights into disease pathogenesis and biology.

Autoantibody testing: practical considerations

Commercial testing for specific onconeuronal antibodies is typically performed using immunodot or blot methodologies.[32,33] With these techniques, the antigen(s) of interest are immobilised within a fixed band on a nitrocellulose paper, patient serum or CSF is applied and if 'antibody-positive' an intensity is visualised at the known location of the antigen (**Figure 1**). Several recent studies have cast doubt on the accuracy of this approach, consistently showing only ~40% of line blot positive results are verified by more robust methods such as immunofluorescence or cell-based assays.[32,33] Positive predictive values have been as low as 39%.[34] Whilst bleak, these overall results mask some even more worrying findings for individual antigens – for example, Dechelotte *et al* almost never confirmed positive line dots for amphiphysin-, Ma1- and Yo-antibodies, whereas for Hu-antibodies, confirmation by other methods was observed in up to ~88%.[33] A recent investigation into patients with collapsin response-mediator protein-5 (CRMP5)/CV2-antibodies showed commercial kits failed to detect ~8% of patient sera found positive by immunofluorescence or cell based assay (**Figure 1**).[35] Two of these samples were from individuals with SCLC, showing a crucial diagnosis could have been missed.

Therefore, expert consensus suggests that a positive onconeuronal result by commercial kits should be reinforced by a second method, and that both positive and negative results are

interpreted in the context of the patient presentation. Research laboratories with an interest in these disorders and routine laboratories with close links to experienced clinicians may be able to help with difficult cases. The importance of research level assays is further emphasised by the rapid expansion of in newer entities (e.g. Kelch-like protein 11; KLHL11), for which availability remains on a research-only basis despite its description in 2019.[36] Overall, to maximise sensitivity and specificity, we recommend sending both serum and CSF for antibody testing as both biosamples show differering diagnostic characteristics across CNS autoimmune illnesses and, in combination, provide optimised diagnostic accuracy.[37]

Practical approach to testing: which antibodies should I suspect…

...at the population level

Among 979 cases in a 2010 European cohort, the most frequently detected antibodies were against Hu (~39%), Yo (~13%), CRMP5/CV2 (~6%) and Ri (~5%). The rate of seronegative PNS in the cohort was ~18%, and – overall - the most common tumours were SCLC (~38%), ovarian (~10%) and breast (~9%).[3] More recently, a 2020 population-based Italian study identified Yo (30%), Hu (26%), and Ma2 (22%) as the leading antigenic specificities.[1] Overall, these authors found PNS coexisted with 1 in 334 cancers, most commonly lung (17%), breast (16%) and lymphoma (12%).Modest variations between these two cohorts may be ascribed to ancestry, chronological trends or local environmental factors. However, it is important to note that, although some are especially typical, a variety of tumours can be associated with PNS (**Tables 1 and 2**).

…if my patient has (forms of) encephalitis

Onconeuronal antibodies which target the 'Hu' antigens are classically associated with a limited 'limbic' encephalitis (LE). These patients can also develop a multifocal neurological presentation, including cord involvement and rhombencephalitis.[23] A striking peripheral manifestation is a sensory neuronopathy, with clinical and electrophysiological studies also demonstrating sensory or sensorimotor neuropathies.[23,38] Typically, patients are in their mid-60s with a slight male predominance, but Hu-antibodies also have been detected in children with neuroblastoma in connection with a brainstem syndrome including opsoclonus-myoclonus [28,39] and an aggressive - but non-paraneoplastic – paediatric LE with a limited response to immunotherapies.[39]

A number of surface neuronal antibodies associate with autoimmune encephalitis and tumours. Again, these patients show clinical characteristics which help refine the pre-test probabilities of a tumour. In addition to the age/sex bias of teratomas in patients with NMDAR-antibody encephaltis, in patients with Morvan's syndrome and contactin-associated protein-like 2 (CASPR2)-autoantibodies a 40% rate of thymoma compares to a <5% rate in patients with CASPR2-autoantibodies and LE.[40] A diencephalic/brainstem-centred encephalitis is a hallmark of the Ma-antibodies, particularly antibodies to Ma2, also known as Ta. Almost all affected patients are male and commonly have testicular germ cell tumours. A distinctive aspect of this disease localises to the hypothalamus with features including gelastic seizures and daytime somnolence (~30%), and even frank narcolepsy/cataplexy.[18,41]

KLHL11-antibody encephalitis was first described as a rhombencephalitis with prominent features of vertigo, diplopia, dysarthria, ataxia and auditory dysfunction (tinnitus and sensorineural hearing loss). The syndrome was originally described exclusively in men with a typical age of onset in the mid-40s and a strong association with testicular tumours (~65%). An early association has been proposed with the class II HLA alleles DQB1*02:01 and DRB1*03:01.[36,42] By contrast, a laboratory-based study using only a cell-based assay, detected KLHL-11 positivity in equal proportions of males and females with a wider phenotype plus both isolated germ cell tumours and in patients with NMDAR-antibody encephalitis.[43] Hence, the full clinical spectrum associated with KLH11-antibodies requires further study.

…if my patient has prominent psychiatric features

NMDAR-antibody encephalitis is the exemplar of antibody-mediated neuropsychiatry and its most prominent characteristics include behavioural change (68%), psychosis (67%), mood disturbances (47%), catatonia (30%), and sleep disturbances (21%).[7] Initial presentation to psychiatric services remains common and patients may have received prior erroneous diagnoses of primary psychosis, bipolar disorder or depression. Diagnosis should be suspected in new onset acute to sub-acute psychopathology, especially in young women (~80%), typically with neurological accompaniments such as memory disturbances, seizures and/or movement disorders.[44–47]

The Ophelia syndrome is associated with surface-directed mGluR5 antibodies and seen in patients with Hodgkin lymphoma. Psychosis, hallucinations, mood disorder, behavioural and personality change and sleep disturbance are among the psychiatric features reported.[48] Overall, we recommend antibody screen in new-onset pyschosis in individuals fitting the above descriptions, as well as others with atypical demographic, phenotypic or cinical features compared to primary psychiatric diagnostic categories, in particular the presence of additional traditionally 'neurological' features.

…if my patient has a cerebellar syndrome

A number of onconeuronal antibodies are strongly associated with paraneoplastic cerebellar degeneration (PCD). In PCD, the deterioration is usually acute to subacute, pancerebellar - causing limb and truncal ataxia plus nystagmus and is frequently irreversible - even with successful treatment of the underlying neoplasm - likely secondary to established Purkinje cell destruction.[6,49,50]. A cerebellar ataxia developing over the time course of a neurodegenerative process is rarer, but can be observed in patients with anti-Ri or anti-GAD (glutamic acid decarboxylase) antibodies, although the latter is rarely tumour-associated.[51,52] Yo-antibodies are the most well-established association of a subacute cerebellar syndrome, almost always occuring in women with breast or gynaecological tumours,[6,49] but one case series reports seven men, five of whom had gastro-intestinal malignancy.[53] Also, PCD is reported with Zic4 antibodies, frequently detected alongside other onconeural antibodies in SCLC,[21] and with Tr-antibodies, which are mainly detected in male patients with Hodgkin Lymphoma.[50] Further, around 20% of patients with Hu-antibodies develop a cerebellar syndrome,[23] in addition to ~60% of those with Ri-antibodies, particularly women with breast cancer.[51] Also to be considered in this setting are Ma1-antibodies (between 27-77% in small cohorts),[54,55] CRMP5/CV2-antibodies [56] and mGluR1-antibodies, the latter with superadded psychiatric and cognitive features.[57] Finally, a subgroup of patients with voltage gated calcium channel antibodies (VGCC, P/Q type) have ataxia with SCLC, both with and without Lambert-Eaton myasthenic syndrome (LEMS).[58]

…if my patient has another movement disorder

Ri-antibodies have been described in combination with opsoclonus-myoclonus,[59] and, more recently, movement disorder presentations including tremor, parkinsonism and stiff person syndrome, mainly in female (~80%) patients. Some displayed a stepwise progression and were misdiagnosed with atypical Parkinson's disease, multiple sclerosis or a functional disorder.[51] An important 'not-to-miss' association of Ri-antibodies is jaw dystonia and laryngospasm, which may be severe enough to precipitate nutritional deficiency or airway compromise including sudden death.[60] Also, amphiphysin antibodies are associated with a paraneoplastic stiff person syndrome and a female bias (~60%).[61] Whereas, chorea should prompt consideration of CRMP5/CV2-antibodies which show a male bias (~75%).[56,62] Other presentations of these antibodies are described in **Table 1.** Autoantibody-associated movement disorders been reviewed elsewhere and provide valuable clues as to the nature of the autoimmune illness.[63]

…if my patient has a peripheral nerve or muscle problem

Two classic peripheral PNS are the sensory neuronopathy (or Denny-Brown syndrome) and LEMS.[5] More than 50% of Hu-antibody patients have a sensory neuronopathy or peripheral neuropathy, characteristically involving both large and small fibres with dominant axonal involvement and only upper limb involvement in ~25%,[23,38][38] with or without additional neurological features. The neuropathy occurring in connection with amphiphysin antibodies may be immunotherapy-responsive, increasing the urgency of early and accurate detection.[64] In CRMP5/CV2-antibody disease, the neuropathy is often a painful, asymmetrical, sensorimotor polyradiculopathy which may be steroid-responsive and commonly found alongside additional features such as cerebellar ataxia and myelopathy.[65]. A few (~10%) women with Yo-antibodies may present with a peripheral neuropathy of upper limb onset,[66] and a painful peripheral neuropathy is recognised in association with CASPR2-autoantibodies.[40]

LEMS is accompanied by VGCC-antibodies in ~85% of patients, and is paraneoplastic in ~70%.[67] SOX1-antibodies are a useful biomarker of malignancy in patients with LEMS, being found in as many as ~60% of tumour cases but far less commonly in non-paraneoplastic cases.[68] Paraneoplastic myeloneuropathy[69] is s syndromic description associated chiefly

with antibodies to amphiphysin, Hu and CRMP5/CV2, and in smaller numbers with other specificities (**Table 1**).

….if my patient has lymphoma

Whereas LE (e.g. with mGluR5-antibodies) and PCD (e.g. with antibodies to Tr/DNER or mGluR1) mainly occur with Hodgkin lymphoma, [48,50,57] the more frequent associations of non-Hodgkin lymphoma are sensorimotor neuropathies and dermatomyositis, although Tr/DNER and Ma2 specificities have been encountered.[70,71] It is noteworthy that histopathological efforts did not find DNER was expressed by the malignant cells of Hodgkin lymphoma, suggesting these patients represent a potential exception to the paradigm of tumour-driven immunisation.[50]

...if my patient has dysautonomia

Dysautonomia can cause potentially dangerous complications in several of the paraneoplastic syndromes. For example, in Ri-antibody patients, dysautonomia may lead to cardiac arrhythmias and central respiratory failure.[51] Another manifestation is gastric pseudo-obstruction, especially seen with Hu-antibodies.[5]

Of the surface neuronal mediated antibodies, the autonomic features of LEMS typically include symptoms of dry mouth/eyes, visual disturbance, erectile dysfunction, constipation, impaired sweating and orthostatic hypotension, and are rarely life-threatening.[72] Dysautonomia is a prominent feature of patients with NMDAR-antibodies. This tends to be seen in ~50% and characteristically becomes apparent 2-4 weeks into the illness, with manifestations including tachy-bradycardia, labile blood pressure and cardiac asystole.[45–47] Finally, almost all (>90%) patients with Morvan's syndrome, seen with CASPR2 +/- LGI1 autoantibodies, have dysautonomia, most commonly hyperhidrosis (>85%) and cardiovascular instability (tachycardia, labile blood pressure in ~50%).[40]

…in cases of visual loss

Among their many manifestations, antibodies to CRMP5/CV2 are a recognised association with paraneoplastic optic neuropathy, as well as posterior uveitis.[56,62] Other antibodies can be more associated purely with visual syndromes. For example, melanoma-associated

retinopathy (MAR) has a characteristic presentation of night blindness, photopsias and reduced visual acuity, occurs mainly in patients with a pre-existing diagnosis of cutaneous melanomas, and its appearance may signal a relapse. Onset can be abrupt and antibodies are found to bipolar layer retinal cells, with – as yet – undefined targets.[73] Another syndrome with antibodies to retinal tissue, recoverin or cancer-associated retinopathy (CAR), causes painless visual loss in patients with known cancer of various types (**Table 1**), as well as in some non-paraneoplastic cases.[74,75]

Paraclinical investigations: systemic

Early recognition of a paraneoplastic aetiology is vital to guide oncological investigation and optimise tumour management, which is also a cornerstone in addressing the associated PNS.[72] Imaging forms the mainstay of care – as directed by the clinico-serological association (**Tables 1-3**). Tumour markers (e.g. CA125 where ovarian cancer is suspected) may also be measured, especially when tumours are small and not definitively detected with imaging.[6] As an overview, recommendations suggest body imaging to include CT of the chest, abdomen and pelvis,[72] with additional - more focused - modalities based on the specific predicted associations. For example, testicular ultrasound in men with Ma2-antibodies [41] or pelvic/transvaginal ultrasound or MRI in young women with NMDAR-antibody encephalitis.[37]. Selection of ultrasound or MRI to visualise an ovarian teratoma depends on local expertise and the mental state of patients, who are often extremely agitated in the acute phase of their illness. In our experience, some ovarian teratomas can be radiologically small and challenging to detect (**Figure 2**). Expert radiological help is strongly recommended with equivocal scans. However, without a radiological suggestion of a teratoma, we do not recommend empirical opphrectomy as overall yields appear low from international experiences. In some cases, such as women with subacute cerebellar ataxia, confirmed circulating anti-Yo and negative radiological explorations, a surgical examination may be warranted.[72]

To detect delayed tumour presentations, it is often recommended to follow up a negative body CT with FDG-PET scan and surveillance imaging for several years thereafter.[72] This decision – and the duration of follow-up - should rest with clinical acumen and perceived likelihood of detecting a tumour.

Paraclinical investigations: neurological

CSF

CSF is recommended to explore important differentials. In certain syndromes, such as NMDAR-antibody encephalitis, CSF is highly specific and so helps to confirm the diagnosis.[37] In most of the antibodies discussed within this review, CSF parameters are abnormal (**Table 3**) with common themes including lymphocytic pleocytosis, CSF-specific ('unmatched') oligoclonal bands and elevated protein. Over the range of these conditions, glucose is usually normal and cytospin does not reveal malignant cells (**Table 3**). CSF autoantibodies are frequently detected.[37,76–78] One notable aspect in Ma2-antibody encephalitis is the possible finding of reduced hypocretin in patients with narcolepsy/somnolence.[41] However, it should be highlighted that a bland CSF does not rule out PNS and, in certain entities, such as CASPR2-autoantibodies with Morvan's and $GABA_A$-receptor encephalitis, is quite often unremarkable (**Table 3**).

Neuroimaging

MRI appearances of the brain or spinal cord are often characteristic in particular syndromes (**Table 3**). For example, abnormalities in hypothalamus, diencephalon and rhombencephalon in patients with Ma2-antibody encephalitis,[41] basal ganglionitis in those with chorea and CRMP5/CV2-antibodies,[79] and multifocal cortical and subcortical abnormalities in patients with $GABA_AR$-antibodies.[80] In the spinal syndromes, paraneoplastic myelopathies often show a predominance for corticospinal tracts and are frequently longitudinally extensive.[81] Sometimes, brain MRI in Ma2-antibody encephalitis is particularly challenging because contrast enhancement are frequent and all the MRI parameters can imitate brain lymphoma.[41]

Again, it is important to note that MRI brain and spine can be normal in PNS. This is an especially common scenario in NMDAR-antibody encephalitis,[45,46] in patients with amphiphysin antibodies,[51] and in Morvan's syndrome with CASPR2-autoantibodies.[40] Therefore, in a clinically and serologically appropriate setting, an unremarkable MRI should not deter from the diagnosis. Moreover, in most cases of PCD, initial MRI or CT is unrevealing with cerebellar atrophy only visible in later scans (**Figure 3**).

Electrophysiology

Patients with encephalopathies will typically manifest electrophysiological abnormalities (**Table 3**). One distinctive EEG pattern is extreme delta brush in NMDAR-antibody encephalitis [82] – but is usually apparent only in the profoundly encephalopathic patient, hence having limited diagnostic value.[45] An EEG study in Hu-antibody patients demonstrated surprisingly widespread abnormalities including in those without overt seizures or focal clinical signs.[83]

EMG is a valuable investigation in patients with CASPR2-autoantibodies where frank neuromyotonia is common.[40,84] Peripheral neurophysiology in paraneoplastic-mediated neuropathies may delineate relevant findings as described above, but less specific findings of sensory or sensorimotor neuropathy are also possible (**Table 2**). In suspected LEMS, decreased compound muscle action potentials (CMAPs) are anticipated; and the electrical hallmark is increment after high frequency repetitive nerve stimulation.[72] Specific abnormalities consistent with bipolar cell dysfunction on electroretinogram (ERG) may assist in the diagnosis of patients with MAR-antibodies.[73]

Outcomes

Tumour identification and appropriate oncological management is key to medical and neurological stabilisation, especially as many PNS associated with cancers display a limited immunotherapy response.[72] Median survival is frequently aligned to the underlying tumour prognosis and delineated for the individual antibodies within **Tables 1 and 2.** However, the PNS field is limited by small and highly selected cohorts, few randomised trials and reports of spontaneous improvement, which all bias interpretations of treatment benefits.[85] An analysis of deaths in 403 paraneoplastic patients with differing antibody specificities, concluded that 109 (27%) died of their neurological syndrome, 150 (37%) of tumour progression and the remainder of unknown or other causes. The risk of death from the paraneoplastic syndrome was highest for patients with dysautonomic features; in this subgroup nearly 60% died of neurological disease.[3] It has also been shown in more than one comparative observational cohort study that patients with Hu-antibodies have a worse prognosis than those with CRMP5/CV2-antibodies.[56,65]

Treatment and immunotherapy outcomes: onconeuronal antibodies

While many cases with onconeuronal antibodies are immunotherapy-resistant or only partially responsive, it is important to recognise certain syndromes in which there is stronger evidence for immune-directed treatment. For example young men with Ma2-antibodies and testicular cancer may attain some recovery with tumour removal and immunotherapy,[41] and an immune therapy response is also documented in CRMP5/CV2- and amphiphysin-antibody associated neuropathies.[64,65] Women with amphiphysin-antibody stiff person syndrome can also make worthwhile functional gains with cancer treatment and steroids.[86] On the other hand, there is limited evidence for a symptomatic benefit of immunotherapy in Hu-antibody neuropathy, and the main predictors of outcome among all patients with this specificity are disability / performance status, age, and multifocal disease.[23] One trial of triple immunotherapy (intravenous methylprednisolone, intravenous immunoglobulin and cyclophosphamide) in patients with Hu- and Yo-antibodies harbouring a variety of presentations achieved transient stabilisation in neuropathy patients but no improvement in other symptomatic groups.[87] Similarly disappointing results were achieved in a trial of IVIG alone.[88] Many cases of PCD remain refractory to treatment even if the underlying malignancy is successfully addressed, a situation which is particularly observed with Yo-antibodies.[6,49,66] Treatment response in some of the rarer syndromes is available only in case reports but there is some suggestion that rituximab is efficacious in some patients with Zic4-antibodies.[89] The literature for treatment in paraneoplastic retinopathies is dominated by case reports, but it is generally believed that in CAR cancer treatment alone is ineffective for visual recovery, and that additional immune treatments are beneficial.[90]

Treatment and immunotherapy outcomes: surface neuronal antibodies

In marked contrast, overall, the vast majority of surface neuronal antibody patients are immunotherapy-sensitive. In addition to oncological management, these patients merit a trial of immunotherapy, often extending to second- or even third-line agents based on iniital responses (**Table 2** ; Uy, Binks and Irani, Practical Neurology *in press*). More than 80% of treated NMDAR-antibody encephalitis can be expected to have a good outcome at 24 months, [46] a figure likely to have increased since better recognition and more effective treatment protocols are common place. Paraneoplastic and non-paraneoplastic cases are likely to do equally as well, but shorter time to oophorectomy is key in securing clinical improvement in

patients with a teratoma.[45] In our experience, this benefits from close multidisciplinary discussions with radiology and gynaecology colleagues with a balance of considerations regarding fertility preservation in young women of child-bearing potential.

A contrasting situation is seen in patients with CASPR2-autoantibodies, where patients with thymomas have demonstrably worse outcomes compared to non-paraneoplastic patients.[40] In this observational cohort, the mortality rate of the thymoma group was 50%, mainly due to tumour-related causes such as respiratory failure and tumour invasion, and mRS was static despite immunotherapies. However, recently in our centres, we have experienced some clinical benefits with rituximab in such patients (Irani and Honnorat, unpublished observations).

The syndromes associated with surface antibodies to mGluR1 and mGluR5, despite common associations with lymphoma, are typically immunoresponsive and >50% of mGluR5-autoantibody patients can be expected to make a full recovery.[48,57] In VGCC-antibody positive patients, the LEMS - but less so the cerebellar syndrome - responds to immunotherapy and 3,4-diaminopyridine can be used for symptomatic treatment.[72] A report of global improvement following rituximab of a VGCC patient with LEMS and cerebellar degeneration again highlights the possible opportunities of newer therapies in recalcitrant disease entities.[91] Within this group, the poorest outlook is reserved for patients with $GABA_B$ receptor autoantibodies, whose functional improvement is in many cases partial and, despite immunotherapy gains, many die due to an underlying SCLC and its related complications.[76,78]

Conclusions

- Early recognition of paraneoplastic syndromes is crucial for successful identification and management of the underlying tumour
- Serum results should be interpreted with a critical, clinical eye given the pitfalls of lineblot/immunodot testing
- Oncological treatments offer the best chance of a good outcome in most cases

- Syndromes mediated by surface neuronal autoantibodies are in most cases responsive to prompt immunotherapy; some syndromes secondary to onconeuronal entities may not be, but there are important exceptions
- High-quality evidence is lacking, meaning much practice is based on observational or cohort studies

Further reading

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Competing Interests

SRI is a co-applicant and receives royalties on patent application WO/2010/046716 (U.K. patent no., PCT/GB2009/051441) entitled 'Neurological Autoimmune Disorders'. The patent has been licensed commercially for the development of assays for LGI1 and other VGKC-complex antibodies. SRI and SB are co-applicants on a patent application entitled “Diagnostic Strategy to improve specificity of CASPR2 antibody detection” (PCT/GB2019/051257, publication number WO/2019/211633 and UK1807410.4). SRI has received honoraria from UCB, MedImmun, ADC therapeutics and Medlink Neurology, and research support from CSL Behring, UCB and ONO Pharma. CU and JH declare no competing interests with respect to this publication.

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Data sharing statement

Not applicable

Figure legends

Figure 1: Detection of paraneoplastic antigens. Use of commercial line or dot blots miss clinically relevant reactivities identified by immunohistochemistry or cell-based assay. **A:** Immunohistochemistry on sections of paraformaldehyde-perfused rat cerebellum incubated with a CV2-positive serum (dilution 1:5000) that did not react with commercial immunoblots despite robust immunoreactivity with the cytoplasm and processes of oligodendrocytes in the granular cell layer (GCL) and white matter (WM). Scale bar=25 µm. **B:** Line blot neuronal antigen profile. Antigens by columns: a: Titin, b: SOX1, c: Recoverin, d: Hu, e: Yo, f: Ri, g: Ma2, h: CV2, and i: Amphiphysin. Strips were incubated with the sera of patients with CV2-

antibodies determined by immunohistochemistry, two positives and one negative control. Serum 3 showed very mild immunoreactivity at 1/200 dilution but was negative at the manufacturer's recommended dilution (1/1000). This serum was also immunoreactive with amphiphysin. **C:** Serum of patients with CV2-antibodies by immunohistochemistry, diluted at 1/2000 and 1/200, did not react with blot strips. The localization of the appropriate CV2 band detected with the positive control (+) is indicated with an arrow head. Serum 3 showed a weak immunoreactivity with SOX1 and amphiphysin. **D:** HEK293 cells transfected to express green fluorescent protein (GFP)-tagged CRMP5 were incubated with serum of patients with CV2-antibodies that did not react with commercial immunoblots or control (−) serum. Patient's serum, but not control serum, stained the cells (red) that specifically express CRMP5 (seen in green). Both reactivities are shown merged in the bottom row (yellow). Nuclei counterstained with DAPI. Scale bar = 20 µm. Reproduced from [35] with permission from Elsevier.

Figure 2: Body imaging in paraneoplastic encephalitides. A-B: Pelvic MRI of a 19 year old female with N-methyl-D-aspartate receptor-antibody encephalitis. A right ovarian teratoma is visible as a dark cystic area (arrow) on a fat suppressed sequence (A). This was previously visualised on T1 imaging (B) (arrow) but required fat suppressed sequences for the lesion to be clearly identifiable as a dermoid, rather than haemorrhagic, cyst.

Figure 3: CNS imaging in paraneoplastic encephalitides. A: CT head showing chronic cerebellar atrophy in a patient with Yo-antibodies **B-D:** FLAIR hyperintensities in a patient with AMPAR-antibody encephalitis with a thymoma. The images demonstrate multifocal inflammatory T2 hyperintensities of bilateral hippocampi with other discrete cortical lesions in the right orbitofrontal cortex, left anterior cingulate, right posterior superior temporal sulcus, right anterior and inferior insula, right temporal operculum, left posterior temporal region, left occipital and left calcarine cortex. **Abbreviations**: AMPAR: α-amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid receptor; FLAIR: fluid-attenuated inversion recovery

Table 1: Demographic, tumour, clinical, treatment response and prognosis in onconeuronal-antibody associated syndromes

Antibody (alternate names)	Demographics & tumour frequency	Main associated tumour types	Predominant associated syndromes	Immunotherapy responsive?	Life expectancy
Hu (ANNA-1) [23,38,56,69]	Median age 60s, men ~75% Tumour frequency up to 98% with four year follow-up after onset of paraneoplastic syndrome	Small cell lung cancer (SCLC) in ~ 75% Others include: other lung, prostate, breast, bladder, gastro-intestinal (GI) tract, ovary, neuroendocrine, unknown origin	Sensory neuropathy (~50%), of which sensory neuronopathy ~30% Cerebellar ataxia / paraneoplastic cerebellar degeneration (PCD) (~20%) Limbic or cortical encephalitis (up to ~20%) Rhombencephalitis (up to ~20%) Sensorimotor neuropathy (~5%) Autonomic dysfunction (up to ~24%) Multifocal deficits (~20%) Myeloneuropathy – newly reported	Limited evidence of symptomatic benefit with early use in patients with sensory neuropathy, no evidence of survival benefit	Median survival ~11.8 months in a cohort with ~80% receiving oncological treatment and ~45% immunotherapies (IT)
Yo (PCA-1) [6,49,53,66,69]	Almost always women with median age 60s, and at least ~90%-100% tumour	Breast (~20%) Gynaecological (ovary/fallopian tube ~60%) Rarely in men: upper GI adenocarcinoma or prostate	PCD (at onset or within disease course ~90%) Peripheral neuropathy (10%) Myeloneuropathy – newly reported	No evidence of sustained symptomatic or survival benefit	Overall median survival ~24 months. An analysis of 25 oncologically treated patients showed survival significantly longer in breast (~100 months) than ovarian (~22 months) cancers
Ri (ANNA-2) [51,60]	Mainly (~80%) women, median age mid-60s, ~90% with a tumour	Mainly breast (up to 70%) and lung (up to 25%)	Cerebellar syndrome (~66%) Opsoclonus +/- myoclonus (~30%) Dystonia and Parkinsonism, ~20% each; with jaw dystonia specifically up to 20% depending on cohort	Reports of improved jaw dystonia with early aggressive cancer/IT No evidence of survival benefit in a mixed cohort	Survival ~70% at 12 months, ~60% at 24 months, and ~50% at 36 months, with all patients receiving anti-tumour therapy and 58% immunotherapy
Ma1 (PNMA1 & 2) [54,55]	Male ~40-75%, median age ~60, tumour in 77-100%, cohort dependent	Various including lung/pleural (~30%), testicular, GI tract, non-Hodgkin lymphoma, breast, renal and melanoma	Limbic and/or brainstem encephalitis ~45-65% Cerebellar/ brainstem syndrome (up to ~75%) Peripheral neuropathy ~10%	Little or no effect of IT on outcomes	Reported in small cohorts only, 36-38% death due to tumour or neurological progression with oncological/immunotherapy in ~50% where ascertainable
Ma2/Ta (PNMA2 only) [24,41,54,55]	Consistently ~75% male, median age younger in male (mid-30s) than mixed or female (early 60s) cohorts, tumour ~90%	Most commonly testicular germ cell (up to ~70%) or lung tumours (non SCLC)	Encephalitis – limbic, diencephalic, and/or brainstem (95%) but 'classic' limbic ~25% Distinctive aspects include excessive daytime sleepiness (~30%) and eye movement abnormalities in encephalitis patients (~90%)	Good tumour and syndrome response to orchidectomy +/- IT (steroids, IVIG, plasma exchange) esp. men <45	14% death reported in one cohort of 28 patients (treatment details not specified)
Amphiphysin [61,64,69,86]	M:F 40:60, higher F (~90%) in neuropathy, mean age ~65, malignancy in ~80% (in patients with only amphiphysin antibodies)	Lung cancer (mainly SCLC) ~70%, breast cancer ~25%	Common associations include neuropathies (~60%) and stiff-person-spectrum disorders (~30-40%), but also myelopathy, encephalitis/encephalopathy, cerebellar ataxia and myeloneuropathy	Reported with chemotherapy and steroids in stiff person syndrome, and with IT especially cyclophosphamide in neuropathy	In mixed phenotypes, survival ~7-9 months, ~50% of patients receiving oncological and/or immunotherapy; in mainly treated neuropathy cases ~30% mortality at 5 years

Zic4 [21,89]	Median mid-60s, nearly 90% male, ~90% with tumour (in patients with only Zic4 antibodies and no other immunities)	SCLC in ~90% of patients with Zic4 +/- other immunities	PCD most common in both isolated Zic4 and Zic4 + other onconeuronal antibodies	Limited to case reports, ~50% of which improved with chemotherapy + IT, including Rituximab	Not systematically reported
KELCH11 (KLHL11) [36,42,43]	In clinical cohorts, all patients are male, with median age mid-40s, and cancer found in ~70%	~65% testicular cancer (mainly seminoma) in clinical cohorts. In serological studies, also found with teratoma (ovarian or testicular) and NMDAR-Ab-E	Rhombencephalitis, with ataxia (~80%), diplopia (~60%), vertigo (~50%) and auditory symptoms (hearing loss and tinnitus ~40% each, tinnitus often an early manifestation), dysarthria (~30%), and seizures (~20%)	~60% achieved neurological improvement or stability with IT, trend to better outcomes with testicular cancer	~25% mortality at median of 55 months in a cohort in which almost all received oncological and IT
mGluR1 [57] mGluR5 [48]	Median age ~55, ~2:1 M:F, ~11% with tumour Median age ~30, including paediatric cases, M=F, ~60% with tumour	Hodgkin lymphoma, cutaneous T lymphoma Hodgkin lymphoma, SCLC	Cerebellar syndrome (~90%) + cognitive/psychiatric features Neuropsychiatric and cognitive deficits, poor sleep, seizures; Ophelia syndrome	With IT, ~50% stabilisation and ~40% improvement Complete recovery in more than 50%, mostly treated with cancer +/- immunotherapy; relapse responded to same	2/25 published patients, mainly IT-treated, died No deaths in a contemporary cohort
Tr/DNER [50,71]	Median age ~60, ~80% male	Hodgkin Lymphoma (~90%), occasionally also Non-Hodgkin Lymphoma	Predominantly a cerebellar syndrome, frequently pure in Hodgkin Lymphoma	Often irreversible. Remission in ~15% of patients mainly under-40 treated for HL (no non-tumour patients improved)	No systematic data; in one small observational cohort 2/16 patients with a cerebellar syndrome and HL, of which 10 with Tr/DNER, died
CV2/CRMP5 [56,62,65]	Median age ~60, ~75% men, ~90% tumour	SCLC and thymoma	Varied including neuropathy (largely an asymmetric painful polyradiculopathy), cerebellar ataxia, chorea, uvea/retinal involvement, LEMS, myeloneuropathy	Neuropathy may be responsive to high dose IV steroids	Median survival 48 months if CRMP5/CV2 antibodies in isolation, death in ~40%
LEMS - VGCC: P/Q type [58,67,92] LEMS - Sox1 (AGNA1) [68,93]	In paraneoplastic and non-paraneoplastic LEMS median age is in the early 60s, ~70% of LEMS have underlying cancer and ~2/3 paraneoplastic patients are male	SCLC	Patients with VGCC antibodies may present with LEMS alone, or LEMS + PCD; VGCC antibodies may also denote ataxia without LEMS in ~40% lung cancer PCD Sox1 Indicates paraneoplastic LEMS (seen in ~60% paraneoplastic but not in idiopathic cases); background Sox positivity rate of ~20-30% in SCLC +/- Hu antibodies	The myasthenic syndrome, but not the cerebellar syndrome, responds well to IT	Median survival 12 months in PCD patients (mostly with tumour treatment, but some with only immunotherapy or none) With Sox1 positivity, SCLC and LEMS, median survival ~15 months in mostly oncologically treated patients
Retinopathies: MAR [73]	Mean age mid-50s, >80% male	Mainly cutaneous melanoma	Night blindness, photopsias, visual field deficit, and reduced visual acuity	Case series only, benefit in some of varied IT regimes + cytoreduction	Average survival 5.9 years after melanoma onset
Recoverin/CAR: [74,75,90]	Mean age early 60s, ~40-60% women	SCLC, prostate and endometrial cancer, but also found in retinitis pigmentosa	Painless visual loss, uveitis	Cancer therapy alone does not abate visual loss, benefit of various IT in some case reports	Not systematically reported

Abbreviations: AGNA1: anti-glial nuclear antibody; **ANNA**: antineuronal nuclear antibody*;* **CAR:** cancer-associated retinopathy; **CRMP5:** collapsin response-mediator protein-5; **DNER**: delta and notch-like epidermal growth factor-related receptor; **GI**: gastro-intestinal; **IT**: immunotherapy; **IV:** intravenous; **KELCH11**: Kelch-like protein 11; **LEMS:** Lambert Eaton Myasthenic syndrome; **MAR:** melanoma-associated retinopathy; **mGluR1/5:** metabotropic glutamate receptor 1/5; **PCA:** Purkinje cell cytoplasmic antibody; **PCD**: paraneoplastic cerebellar degeneration; **PNMA1/2**: paraneoplastic antigen Ma1/2; **SCLC**; small-cell lung cancer; **VGCC**: voltage-gated calcium channel.

Table 2: Demographic, tumour, clinical, treatment response and prognosis in cell surface antibody-mediated syndromes where an underlying tumour is often detected in a minority of cases

Antibody (alternate names)	Demographics and tumour frequency	Main associated tumour types	Predominant associated syndromes	Immunotherapy responsive?	Life expectancy
NMDA-receptor antibodies [7,44–47]	~80% female, median age 27, ~30% with teratoma	Mainly ovarian teratoma, especially in women <45	NMDAR-Ab-E: psychiatric features, seizures, movement disorder, dysautonomia	Yes, good outcomes with early (<40 days) immunotherapy (IT) (steroids + at least one other immune treatment) and early oophorectomy, in teratoma cases	In a large cohort, of which 94% treated with IT and/or tumour removal, ~5% mortality, almost all patients with mRS 5 before death
$GABA_{A/B}$ receptor antibodies: $GABA_A$ [80]	Male = Female, median age ~40 (but can affect paediatric population), tumour in 60% adults (10% children)	Thymoma	Acute encephalitis with prominent seizures, including status epilepticus and epilepsia partialis continua	Partial or complete (~30%) recovery in ~85% of patients receiving IT	In same cohort death in ~15%, 2/3 status epilepticus, 1/3 sepsis
$GABA_B$ [9,76,78]	Male ~80% and median age mid-60s in paraneoplastic cases (tumour in ~50% of $GABA_B$, often with additional onconeuronal positivities)	SCLC	Limbic encephalitis predominant in paraneoplastic patients	Response of neurological syndrome to immunotherapy in up to ~90% treated paraneoplastic patients, often partial	Median survival of ~15months, death in tumour patients due to cancer progression or chemotherapy complications (death rare in non-tumour patients)
AMPA-receptor antibodies [8]	Median age ~55, women ~70%, tumour in ~50%	Lung, breast, thymus, ovarian	Encephalitis, often severe and acute. Confusion and memory deficits prominent, may present with or without seizures	Median mRS 2 in mainly immunotherapy treated patients; worse outcomes reported in those with fulminant encephalitis	Death occurred in ~50% of the fulminant encephalitis cases, but was rare with other presentations
CASPR2-antibodies [40]	Median age 60s, men ~90%, tumour in up to 40% (Morvan's syndrome)	Thymoma	Morvan's syndrome predominant in paraneoplastic group. Other presentations include limbic encephalitis, cerebellar syndrome, isolated neuromyotonia/myokimia, painful peripheral nerve syndrome	~50% of tumour patients make a neurological improvement on mRS with immunotherapy	~50% death rate among immunotherapy-treated patients with Morvan's syndrome and tumour

Abbreviations: AMPA: α-amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid; **CASPR2:** contactin-associated protein-like 2; **$GABA_{A/B}$**: γ-amino butyric acid (alpha/beta subunit); **IT**: immunotherapy; **NMDAR:** N-methyl-D-aspartate receptor; **NMDAR-Ab-E:** NMDAR-antibody encephalitis; **SCLC**; small-cell lung cancer.

Table 3: Paraclinical features of onconeuronal and surface-antibody associated syndromes

Investigation / Antibody and syndrome	CSF inflammatory (pleocytosis, OCBs)	Intrathecal synthesis ?	CSF antibodies detected	MRI abnormal acute	Temporal lobe high signal	Multifocal/other	Cerebellar atrophy	EEG abnormal	Predominant pattern nerve conduction studies/EMG
Onconeuronal									
Hu (ANNA1) LE									
Hu (ANNA1) BE									
Hu (ANNA1) PCD						Late	Late		
Hu (ANNA1) neuropathy									SN, SMN, A, (D)
Yo (PCA1) PCD							Late		SN, SMN, PRN, A
Ri (ANNA2)									
Ma (PNMA1&2)		(Ma2)	(Ma2)						
Ma2/Ta (PNMA2)									
Amphiphysin		*	*						CMU activity in SPS
Amphiphysin neuropathy									SN, SMN, PRN, A
Zic4	*			*	*	*			
KELCH11									
mGLuR1							Late		
mGLuR5									
Tr/DNER PCD		*					Late		
CRMP5/CV2 mixed					If LE*				SN, SMN, PRN, A
CRMP5/CV2 chorea						BG			Slowing*
CRMP5/CV2 neuropathy									SN, SMN, PRN, A
VGCC LEMS									↓ CMAPs
VGCC PCD					^				LEMS in ~40%
Surface neuronal									
NMDAR-Ab-E									
$GABA_A$									
$GABA_B$									
AMPAR		+							
CASPR2 – Morvan's									Neuromyotonia
CASPR2 - LE		+							Myokimia

Abbreviations: A: axonal; **AMPAR:** α-amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid receptor; **ANNA**: antineuronal nuclear antibody; **BE:** brainstem encephalitis; **CASPR2:** contactin-associated protein-like 2; **CMAPs:** compound muscle action potentials; **CMU:** continuous motor unit; **CRMP5:** collapsin response-mediator protein-5; **D:** demyelinating; **DNER**: delta and notch-like epidermal growth factor-related receptor; **$GABA_{A/B}$**: γ-amino butyric acid (alpha/beta subunit);**GI**: gastro-intestinal; **IT**: immunotherapy; **IV:** intravenous; **KELCH11**: Kelch-like protein 11; **LEMS:** Lambert Eaton Myasthenic syndrome; **mGluR1/5:** metabotropic glutamate receptor 1/5; **LE:** limbic encephalitis; **Morvan's:** Morvan's Syndrome; **NMDAR:** N-methyl-D-aspartate receptor; **NMDAR-Ab-E:** NMDAR-antibody encephalitis **OCBs:** oligoclonal bands; **PCA:** Purkinje cell cytoplasmic antibody; **PCD**: paraneoplastic cerebellar degeneration; **PNMA1/2**: paraneoplastic antigen Ma1/2; **PRN:** polyradicular neuropathy; **SMN:** sensory motor neuropathy; **SN:** sensory neuropathy; **SPS:** Stiff Person Syndrome; **VGCC**: voltage-gated calcium channel.

Table 3 legend: Paraclinical features of onconeuronal and surface-antibody associated syndromes compiled from references cited in this review – key:

- Not delineated
- Usually absent
- Sometimes (up to ~30%)
- Quite frequent (~30-60%)
- Frequent (more than ~60%)

- * Based on small reports (typically ~5 or fewer)
- ^ Isolated case reports of VGCC and LE
- + Tested on a subset of patients