

Paraneoplastic neurological syndromes: a practical approach to diagnosis and management

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ABSTRACT

Paraneoplastic neurological syndromes (PNS) are the immune-mediated effects of a remote cancer and are characterised by an autoantibody response against antigens expressed by the tumour. Classically, well-characterised ‘onconeural’ antibodies target intracellular antigens and hence cannot access their antigens across intact cell membranes. The pathogenic mediators are likely to be neuronal-specific T cells. There is a variable response to immunotherapies and the clinical syndrome helps to direct the search for a specific set of tumours. By contrast, many newly emerging autoantibodies with oncological associations target cell surface epitopes and can exert direct pathogenic effects on both the central and peripheral nervous systems. Patients with these cell-surface directed autoantibodies often clearly respond to immunotherapies. Overall, the clinical, serological and oncological features in an individual patient help to determine the clinical relevance of the syndrome and hence guide its management. 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 and 8/100 000 person-years,^{1,2} indicating ongoing under-recognition. Distinctive clinical and serological features (tables 1–3) typically direct the search for a tumour, which is subsequently detected in around 65% of cases. Rarely this tumour emerges only 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 Among 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 of 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.

PARANEOPLASTIC ANTIBODIES IN CONTEXT

Traditionally, PNS have been associated with ‘well-defined onconeural’ antibodies, which almost always target intracellular proteins and hence show limited direct pathogenic significance. Nevertheless, their presence often indicates a robust (sometimes nearly 100%) association with a tumour in addition to distinct clinical links (table 1), for example, Yo antibodies and cerebellar degeneration.⁶

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

Antibody (alternative names)	Demographics and tumour frequency	Main associated tumour types	Predominant associated syndromes	IT responsive?	Life expectancy
Hu (ANNA-1) 24 38 57 70	Median age 60s, men ~75% Tumour frequency up to 98% with 4-year follow-up after onset of paraneoplastic syndrome	SCLC in ~75% Others include other lung, prostate, breast, bladder, GI tract, ovary, neuroendocrine, unknown origin	Sensory neuropathy (~50%), of which sensory neuropathy ~30% Cerebellar ataxia/PCD (~20%) Limbic or cortical encephalitis (up to ~20%) Rhombencephalitis (up to ~20%) Sensorimotor neuropathy (~5%) Autonomic dysfunction (up to ~2.4%) 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% IT
Yo (PCA-1) ^{6 50 54 67 70}	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 cancer (~100 months) than ovarian (~22 months) cancer.
Ri (ANNA-2) ^{52 61}	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 antitumour therapy and 58% IT
Ma1 (PNMA1 and 2) ^{55 56}	M: ~40%—75%, median age ~60, tumour in 77%—100%, cohort dependent	Various including lung/pleural (~30%), testicular, GI tract, non-HL, breast cancer, renal cancer 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/IT in ~50% where ascertainable
Ma2/ta (PNMA2 only) 25 42 55 56	Consistently ~75% M, median age younger in M (mid-30s) than mixed or F (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%)	Some tumour and syndrome response to orchidectomy±IT (steroids, intravenous immunoglobulins, plasma exchange) especially men<45	14% death reported in one cohort of 28 patients (treatment details not specified)
Amphiphysin 62 65 70 87	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 IT; in mainly treated neuropathy cases—30% mortality at 5 years
Zic4 ^{22 90}	Median mid-60s, nearly 90% M, ~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 onconeural antibodies	Limited to case reports, 50% of which improved with chemotherapy+IT, including rituximab	Not systematically reported
KELCH11 (KLHL11) 31 45 44	In clinical cohorts, all patients are M, 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

Continued

Table 1 Continued

Antibody (alternative names)	Demographics and tumour frequency	Main associated tumour types	Predominant associated syndromes	IT responsive?	Life expectancy
mGluR1 ⁵⁸	Median age ~55, ~2:1 M:F, ~11% with tumour	HL, cutaneous T lymphoma	Cerebellar syndrome (~90%) + cognitive/psychiatric features	With IT, ~50% stabilisation and ~40% improvement	2/25 published patients, mainly IT-treated, died
mGluR5 ⁴⁹	Median age ~30, including paediatric cases, M=F, ~60% with tumour	HL, SCLC	Neuropsychiatric and cognitive deficits, poor sleep, seizures; Ophelia syndrome	Complete recovery in more than 50%, mostly treated with cancer±IT; relapse responded to same	No deaths in a contemporary cohort
Tr/DNER ^{51,72}	Median age ~60, ~80% M	HL (~90%), occasionally also non-HL	Predominantly a cerebellar syndrome, frequently pure in HL	Often irreversible. Remission in ~15% of patients mainly under-40 treated for HL (no patients without tumour improved)	No systematic data; in one small observational cohort, 2/16 patients with a cerebellar syndrome and HL, of which 10 had Tr/DNER, died.
CV2/CRMP5 ^{57,63,66}	Median age ~60, ~75% men, ~90% with tumour	SCLC and thymoma	Varied including neuropathy (largely an asymmetric painful polyradiculopathy), cerebellar ataxia, chorea, uveal/retinal involvement, LEMS, myeloneuropathy	Neuropathy may be responsive to high dose intravenous steroids.	Median survival 48 months if CRMP5/CV2 antibodies in isolation, death in ~40%
LEMS-VGCC: P/Q type ^{59,68,93} LEMS-Sox1 (AGNA1) ^{69,94}	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 M.	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 of 12 months in patients with PCD (mostly with tumour treatment, but some with only IT or none) With Sox1 positivity, SCLC and LEMS, median survival of ~15 months in mostly oncologically treated patients
Retinopathies: MAR ⁷⁴	Mean age mid-50s, >80% M	Mainly cutaneous melanoma	Night blindness, photopsias, visual field deficit and reduced visual acuity	Case series only, benefit in some of varied IT regimens+cytoreduction	Average survival 5.9 years after melanoma onset
Recoverin/CAR ^{75,76,91}	Mean age early 60s, ~40% to 60% women	SCLC, prostate and endometrial cancers, but also found in retinitis pigmentosa	Painless visual loss and uveitis	Cancer therapy alone does not abate visual loss, benefit of various IT in some case reports	Not systematically reported

AGNA1, antitigial 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; F, female; GI, gastrointestinal; HL, Hodgkin's lymphoma; IT, immunotherapy; KELCH11, Kelch-like protein 11; LEMS, Lambert-Eaton myasthenic syndrome; M, male; MAR, melanoma-associated retinopathy; mGluR1/5, metabotropic glutamate receptor 1/5; NMDAR-Ab-E, NMDAR-antibody encephalitis; 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 (alternative names)	Demographics and tumour frequency	Main associated tumour types	Predominant associated syndromes	IT responsive?	Life expectancy
NMDAR antibodies ^{7 45–48}	~80% female, median age 27, ~30% with teratoma	Mainly ovarian teratoma, especially in women aged <45	NMDAR-Ab-E: psychiatric features, seizures, movement disorder, dysautonomia	Yes, good outcomes with early (<40 days) IT (steroids+at least one other immune treatment) and early oophorectomy, in teratoma cases	In a large cohort, of which 94% was treated with IT and/or tumour removal, ~5% mortality, almost all patients had an mRS score of 5 before death.
GABA _{A/B} receptor antibodies: GABA _A ⁸¹	Male=female, median age ~40 (but can affect paediatric population), tumour in 60% of adults (10% children)	Thymoma	Acute encephalitis with prominent seizures, including status epilepticus and epilepsy partialis continua	Partial or complete (~30%) recovery in ~85% of patients undergoing IT	In same cohort death in ~15%, 2/3 had status epilepticus and 1/3 had sepsis
GABA _B ^{9 77 79}	Male ~80% and median age mid-60s in paraneoplastic cases (tumour in ~50% of GABA _B , often with additional onconeural positivities)	SCLC	Limbic encephalitis predominant in paraneoplastic patients	Response of neurological syndrome to IT in up to ~90% of treated paraneoplastic patients, often partial	Median survival of ~15 months, death in patients with tumour due to cancer progression or chemotherapy complications (death rare in patients without tumour)
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 score of 2 in mainly IT-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 ⁴¹	Median age 60s, men ~90%, tumour in up to 40% (Morvan's syndrome)	Thymoma	Morvan's syndrome predominant in the paraneoplastic group. Other presentations include limbic encephalitis, cerebellar syndrome, isolated neuromyotonia/myokymia, painful peripheral nerve syndrome	~50% of patients with tumour had a neurological improvement in mRS score with IT.	~50% death rate among IT-treated patients with Morvan's syndrome and tumour

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; mRS, modified Rankin Scale; NMDAR, N-methyl-D-aspartate receptor; NMDAR-Ab-E, NMDAR-antibody encephalitis; SCLC, small cell lung cancer.

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 amongst PNS. However, the frequency of cancer associated with these newer autoantibodies varies substantially according to 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 occur in young women between ~18 and 35 years of age, 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 cancer (SCLC and thymoma), but mainly in the older patients⁸; and γ -aminobutyric acid (GABA)_B receptor-autoantibodies which associate with a ~50% rate of SCLC in patients more than 50 years of age (table 1).⁹ Also, several surface neuroglial antibodies are associated with very low overall 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/cerebrospinal

Table 3 Paraclinical features of onconeural and surface antibody-associated syndromes

Antibody and syndrome	Investigation	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
Onconeural										
Hu (ANNA 1) LE										
Hu (ANNA 1) BE										
Hu (ANNA 1) PCD							Late			
Hu (ANNA 1) neuropathy								Late		SN, SMN, A, (D)
Yo (PCA 1) PCD										SN, SMN, PRN, A
Ri (ANNA2)										
Ma (PNMA 1/2)			(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										SN, SMN, PRN, A
CRMP5/CV2 chorea						if LE*	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										
AMPA			+							
CASPR2–Morvan's										Neuromyotonia
CASPR2–LE			+							Myokimia

Paraclinical features of onconeural and surface antibody-associated syndromes compiled from references cited in this review—key: ■ not delineated, ■ usually absent, ■ sometimes (up to ~30%), ■ quite frequent (~30% to 60%), ■ frequent (more than ~60%).

+ Tested on a subset of patients.

^ Isolated case reports of VGCC and LE.

* Based on small reports (typically ~5 or fewer).

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; CMAP, compound muscle action potential; CMU, continuous motor unit; CRMP5, collapsin response-mediator protein-5; CSF, cerebrospinal fluid; D, demyelinating; DNER, delta and notch-like epidermal growth factor-related receptor; EEG, electroencephalogram; GABA_{A/B}, γ-aminobutyric acid (alpha/beta subunit); Gi, gastrointestinal; IT, immunotherapy; KELCH11, Kelch-like protein 11; LE, limbic encephalitis; LEMS, Lambert-Eaton myasthenic syndrome; mGluR1/5, metabotropic glutamate receptor 1/5; Morvan's, Morvan's syndrome; NMDAR, N-methyl-D-aspartate receptor; NMDAR-Ab-E, NMDAR-antibody encephalitis; OCB, oligoclonal band; PCA, Purkinje cell cytoplasmic antibody; PCD, paraneoplastic cerebellar degeneration; PNMA 1/2, paraneoplastic antigen Ma1/2; PRN, polyradicular neuropathy; SMN, sensory neuropathy; SN, sensory neuropathy; SPS, stiff-person syndrome; VGCC, voltage-gated calcium channel.

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 neuropathy.
- ▶ Chronic gastric pseudo-obstruction.
- ▶ Lambert-Eaton myasthenic syndrome.
- ▶ Dermatomyositis.

B. Intermediate risk, less 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.

fluid (CSF)—are considered directly pathogenic as they bind *in vivo* and can trigger deleterious effects, including complement fixation, receptor internalisation and induce direct functional modifications to their target proteins.^{11 12} We have detailed these causative antibodies in our sister review.¹³ Also, herein, we will neither focus on autoantibodies in inflammatory myopathies, which have recently been reviewed in this journal,¹⁴ nor the potential triggering of PNS after checkpoint inhibitor drugs,¹⁵ as these likely show different underlying mechanisms to traditional PNS.¹⁶ Myasthenia gravis may be associated with an underlying tumour, typically a thymoma, but also is not further considered herein due to its absence from the updated 2021 guidelines.⁴

PATHOPHYSIOLOGY**Role of onconeural antibodies**

The exact role of intracellular-directed antibodies remains unresolved, but they are unlikely to be direct mediators of disease. Although uptake and pathological effects of Hu-antibodies by Purkinje cells have been shown *in vitro*,¹⁷ their infusion into various *in vivo* models does not consistently replicate disease despite achieving high antibody titres in the experimental animals.¹⁸ Experiments with Ma2-antibodies yielded similar negative results.¹⁹ However, some antibodies classically denoted as ‘onconeural’ 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’s lymphoma and have been recognised to target the extracellular portion of the delta and notch-like epidermal growth factor-related receptor (DNER).²⁰

The relatively high rate of many of these antibodies in patients with tumours but no accompanying neurological syndrome, for example, ~16% of patients with SCLC with Hu-²¹ or Zic4-antibodies,²² and the frequent co-occurrence of more than one paraneoplastic antibody in an individual,³ cautions against interpretation of the antibody result in isolation. It may also suggest that the polyclonal immune response protects against tumour growth. Indeed, tumours may be more indolent in patients with a PNS.²³

In PNS, the likely origin of immunisation is the tumour itself, given immunohistochemical evidence of relevant antigen expression in cancers including SCLC,²⁴ testicular seminoma²⁵ and ovarian carcinoma.²⁶ The accompanying peripheral immune response may translocate to the central nervous system (CNS) in some patients with, overall, CSF studies indicating intrathecal synthesis of antibodies^{6 22 25} in CNS-predominant syndromes (vs absent intrathecal synthesis in those with PNS-only involvement).²⁷ This suggests an influx of lymphocytes to the CSF is a key triggering event for CNS syndromes, a finding that aligns with clonal CD8⁺ T cells and restricted T-cell receptor repertoires in postmortem brain pathology.²⁸ It is likely that these cell types are key disease effectors.

Genetic contributions

Major histocompatibility complex (MHC) molecules are considered essential to antigen presentation, T-cell activation and autoantibody generation. Early—although limited—immunohistochemical observations suggested that tumours of patients with Hu-antibody PNS might have increased expression of MHC proteins, when compared with tumours in patients without autoantibodies.²⁹ More recently, it was demonstrated that patients with Hu-antibody with PNS were significantly more likely to carry the class II molecules HLA-DQ2 and HLA-DR3 than ethnically-matched healthy controls.³⁰ 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 there is a protective effect of DRB1*04:01 across all patients.³¹

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 cerebellar degeneration-related protein 2-like (or Yo) protein. It is plausible that these create neoantigens that drive the disease.²⁶ A differing mechanism has been elucidated in patients harbouring NMDAR-autoantibodies and ovarian

teratoma. Pieces ('explants') of tissue from these—usually benign—tumours, and isolated intratratoma B cells, were able to secrete NMDAR-autoantibodies *in vitro*. Furthermore, tumour immunohistochemistry revealed structures housing T cells, B cells and the NR1 subunit—the key autoantibody epitope.³² 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 map steps along this pathogenic pathway systematically 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 methods.^{33 34} With these techniques, the antigens 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.^{33 34} Positive predictive values have been as low as 39%.³⁵ While bleak, these overall results mask some even more worrying findings for individual antigens—for example, Déchelotte *et al* almost never confirmed

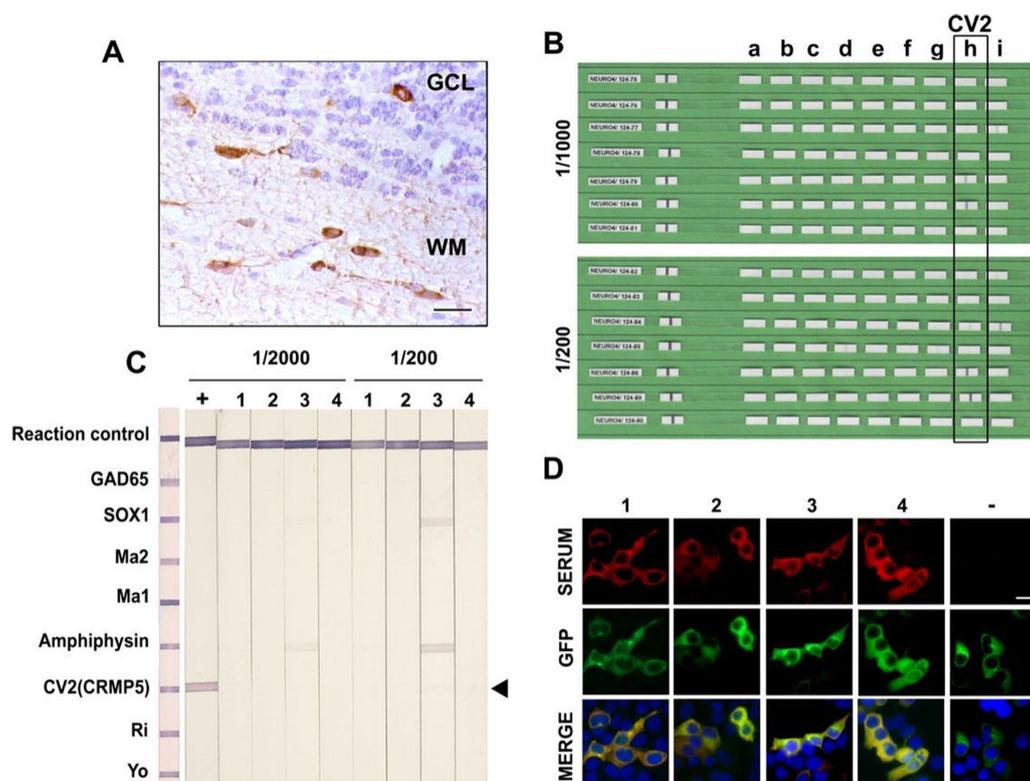


Figure 1 Detection of paraneoplastic antigens. Use of commercial line or dot blots miss clinically relevant reactivities identified by immunohistochemistry or cell-based assay. (A) Immunohistochemistry on sections of paraformaldehyde-perfused rat cerebellum incubated with a CV2-positive serum (dilution 1:5000) that did not react with commercial immunoblots despite robust immunoreactivity with the cytoplasm and processes of oligodendrocytes in the GCL and 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 localisation of the appropriate CV2 band detected with the positive control (+) is indicated with an arrowhead. Serum 3 showed a weak immunoreactivity with SOX1 and amphiphysin. (D) HEK293 cells transfected to express 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 4',6-diamidino-2-phenylindole (DAPI). Scale bar=20 µm. Reproduced from Sabater *et al*³⁶ with permission from Elsevier. GCL, granular cell layer; GFP, green fluorescent protein; WM, white matter.

positive line dots for amphiphysin, Ma1- and Yo-antibodies, whereas for Hu-antibodies, confirmation by other methods was observed in up to ~88%.³⁴ 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).³⁶ Two of these samples were from individuals with SCLC, showing a crucial diagnosis could have been missed.

Therefore, expert consensus suggests that a positive onconeural 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 (eg, Kelch-like protein 11 (KLHL11)), for which availability remains on a research-only basis despite its description in 2019.³⁷ Overall, to maximise sensitivity and specificity, we recommend sending both serum and CSF for antibody testing as both biosamples show differing diagnostic characteristics across CNS autoimmune illnesses and, in combination, provide optimised diagnostic accuracy.³⁸

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 the patient has (forms of) encephalitis

Onconeural antibodies that target the 'Hu' antigens are classically associated with a limited 'limbic' encephalitis. These patients can also develop a multifocal neurological presentation, including spinal cord involvement and rhombencephalitis.²⁴ A striking peripheral manifestation is a sensory neuronopathy, with clinical and electrophysiological studies also showing sensory or sensorimotor neuropathies.^{24 39}

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^{29 40} and an aggressive—but non-paraneoplastic—paediatric limbic encephalitis with a limited response to immunotherapies.⁴⁰

Several surface neuronal antibodies associate with autoimmune encephalitis and tumours. Again, these patients show clinical characteristics that help refine the pretest probabilities of a tumour. In addition to the age/sex bias of teratomas in patients with NMDAR-antibody encephalitis, patients with Morvan's syndrome and contactin-associated protein-like 2 (CASPR2) autoantibodies have a 40% rate of thymoma compared with a <5% rate in patients with CASPR2-autoantibodies and limbic encephalitis.⁴¹ A diencephalic/brainstem-centred encephalitis is a hallmark of 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.^{19 42}

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.^{37 43} By contrast, a laboratory-based study using only a cell-based assay detected KLHL-11 positivity in equal proportions of men and women with a wider phenotype including isolated germ cell tumours and patients with NMDAR-antibody encephalitis.⁴⁴ Hence, the full clinical spectrum associated with KLHL11-antibodies requires further study.

...if the patient has prominent psychiatric features

NMDAR-antibody encephalitis is the exemplar of antibody-mediated neuropsychiatry, and its most prominent characteristics include behavioural changes, psychosis mood disturbances, catatonia and sleep disturbances.⁷ The diagnosis should be suspected in new-onset acute to subacute psychopathology, especially in young women (~80%), typically with neurological accompaniments such as memory disturbances, seizures and/or movement disorders.^{45–48} Initial presentation to psychiatric services remains common, and patients may have received prior erroneous diagnoses of primary psychosis, bipolar disorder or depression.

The Ophelia syndrome is associated with surface-directed mGluR5-antibodies and seen in patients with Hodgkin's lymphoma. Psychosis, hallucinations, mood

disorder, behavioural and personality change, and sleep disturbance are among the psychiatric features reported.⁴⁹

Overall, we recommend antibody screens in new-onset psychosis for individuals fitting the aforementioned descriptions, as well as others with atypical demographic, phenotypical or clinical features when compared with primary psychiatric diagnostic categories, in particular, those with additional traditionally 'neurological' features.

...if the patient has a cerebellar syndrome

Several onconeural antibodies are strongly associated with paraneoplastic cerebellar degeneration. In this condition, 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 50 51} A cerebellar ataxia developing over the time course of a neurodegenerative process is rarer but can be observed, for example in patients with Ri- or glutamic acid decarboxylase- (GAD) antibodies although GAD-antibodies are rarely tumour-associated.^{52 53} Yo-antibodies are the most well-established association of a subacute cerebellar syndrome, almost always occurring in women with breast or gynaecological tumours,^{6 50} but one case series reported seven men, five of whom had gastrointestinal malignancy.⁵⁴ Also, paraneoplastic cerebellar degeneration may occur with Zic4-antibodies, frequently detected alongside other onconeural antibodies in SCLC,²² and with Tr-antibodies, mainly detected in male patients with Hodgkin's lymphoma.⁵¹ Further, around 20% of patients with Hu-antibodies develop a cerebellar syndrome,²⁴ in addition to ~60% of those with Ri-antibodies, particularly women with breast cancer.⁵² Also to be considered in this setting are Ma1-antibodies (between 27% and 77% in small cohorts),^{55 56} CRMP5/CV2-antibodies⁵⁷ and mGluR1-antibodies, the latter with superadded psychiatric and cognitive features.⁵⁸ Finally, a subgroup of patients with voltage-gated calcium channel (VGCC) antibodies (P/Q type) have ataxia with SCLC, both with and without Lambert-Eaton myasthenic syndrome (LEMS).⁵⁹

...if the patient has another movement disorder

Ri-antibodies may occur in combination with opsoclonus-myoclonus⁶⁰ and, more recently, movement disorder presentations including tremor, parkinsonism and stiff-person syndrome, mainly in female (~80%) patients. Some have a stepwise progression and are misdiagnosed with atypical Parkinson's disease, multiple sclerosis or a functional disorder.⁵² 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.⁶¹ Amphiphysin-antibodies are associated with a paraneoplastic stiff-person syndrome and a female bias (~60%).⁶² In contrast, chorea should prompt consideration of CRMP5/CV2-antibodies, which show a male bias (~75%).^{57 63} Table 1 describes other features associated with these antibodies. Autoantibody-associated movement disorders have been reviewed in greater detail elsewhere and provide valuable clues as to the nature of the autoimmune illness.⁶⁴

...if the patient has a peripheral nerve or muscle problem

Two classic peripheral PNS are sensory neuronopathy (or Denny-Brown syndrome) and LEMS.⁵ More than 50% of patients with Hu-antibodies 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%,^{24 39} 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.⁶⁵ 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.⁶⁶ A few (~10%) women with Yo-antibodies may present with a peripheral neuropathy of upper limb onset,⁶⁷ and a painful peripheral neuropathy is recognised in association with CASPR2-autoantibodies.⁴¹

LEMS is accompanied by VGCC-antibodies in ~85% of patients and is paraneoplastic in ~70%.⁶⁸ 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.⁶⁹ Paraneoplastic myeloneuropathy⁷⁰ is a syndromic description associated chiefly with antibodies to amphiphysin, Hu and CRMP5/CV2, and in smaller numbers with other specificities (table 1).

...if the patient has lymphoma

Whereas limbic encephalitis (eg, with mGluR5-antibodies) and paraneoplastic cerebellar degeneration (eg, with antibodies to Tr/DNER or mGluR1) mainly occur with Hodgkin's lymphoma,^{49 51 58} the more frequent associations of non-Hodgkin's lymphoma are sensorimotor neuropathies and dermatomyositis, although Tr/DNER and Ma2 specificities may occur in this context.^{71 72} It is noteworthy that histopathological efforts did not find DNER was expressed by the malignant cells of Hodgkin's lymphoma, suggesting these patients represent a potential exception to the paradigm of tumour-driven immunisation.⁵¹

...if the patient has dysautonomia

Dysautonomia can cause potentially dangerous complications in several of the paraneoplastic syndromes. For example, in patients with Ri-antibodies, dysautonomia may lead to cardiac arrhythmias and central respiratory failure.⁵² Another manifestation is gastric pseudo-obstruction, especially seen with Hu-antibodies.⁵

Of the cell-surface antibodies, autonomic features are prominent in LEMS where they typically include dry mouth/eyes, visual disturbance, erectile dysfunction, constipation, impaired sweating and orthostatic hypotension, and are rarely life-threatening.⁷³ Dysautonomia is a prominent feature of patients with NMDAR-antibodies. This tends to occur in ~50% of cases and characteristically becomes apparent 2–4 weeks into the illness, with manifestations including tachycardia–bradycardia, labile blood pressure and cardiac asystole.^{46–48} Finally, almost all (>90%) patients with Morvan's syndrome, seen with CASPR2- ±LG11-autoantibodies, have dysautonomia, most commonly hyperhidrosis (>85%) and cardiovascular instability (tachycardia, labile blood pressure in ~50%).⁴¹

...if the patient has visual loss

Among their many manifestations, antibodies to CRMP5/CV2 have a recognised association with paraneoplastic optic neuropathy, as well as posterior uveitis.^{57 63} Other antibodies can be more closely associated purely with visual syndromes. For example, melanoma-associated retinopathy has a characteristic presentation of night blindness, photopsias and reduced visual acuity, often occurring 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 against bipolar layer retinal cells, with—as yet—undefined targets.⁷⁴ Another syndrome with antibodies to retinal tissue, recoverin or cancer-associated retinopathy, causes painless visual loss in patients with known cancer of various types (table 1), as well as in some non-paraneoplastic cases.^{75 76}

INVESTIGATIONS

Overall, the early recognition of a paraneoplastic cause is essential to guide oncological investigation and optimise tumour management, which is also a cornerstone in addressing the associated PNS.⁷³ Imaging forms the mainstay of investigations—as directed by the clinico-serological associations (tables 1–3). Tumour markers (eg, 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,⁷³ with additional—more focused—modalities based on the specific predicted associations, for example, testicular ultrasound scanning in men with Ma2-antibodies⁴² or pelvic/transvaginal ultrasound or magnetic resonance

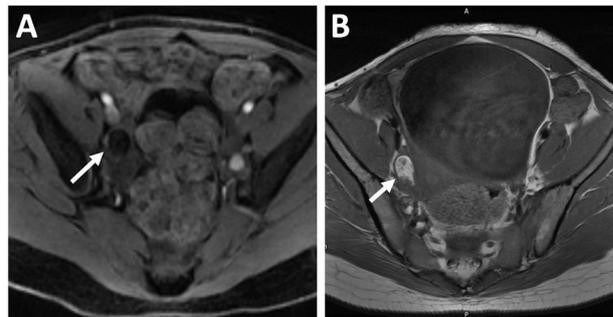


Figure 2 Body imaging in paraneoplastic encephalitis. (A,B) Pelvic MRI of a 19-year-old woman with N-methyl-D-aspartate receptor-antibody encephalitis. A right ovarian teratoma is visible as a dark cystic area (arrow) on a fat suppressed sequence (A). This was previously seen on T1 imaging (B) (arrow)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

(MR) scanning in young women with NMDAR-antibody encephalitis.³⁸ Selection of ultrasound scan 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 the radiological suggestion of a teratoma, we do not recommend empirical oophorectomy as overall yields appear low. In some cases, such as in women with subacute cerebellar ataxia, confirmed circulating Yo-antibodies and negative radiological explorations, a surgical examination may be warranted.⁷³

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.⁷³ This decision – and the duration of follow-up – should rest with clinical acumen and perceived likelihood of detecting a tumour.

Paraclinical investigations: neurological

Cerebrospinal fluid

CSF is recommended to explore important differentials. CSF autoantibodies are frequently detected in PNS.^{38 77–79} In certain syndromes, such as NMDAR-antibody encephalitis, CSF NMDAR-autoantibodies are highly specific and often considered mandatory for a diagnosis.³⁸ In most of the antibodies discussed within this review, broader CSF markers 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). One notable aspect in Ma2-antibody encephalitis is the possible finding of reduced hyporetin in patients with narcolepsy/somnolence.⁴²

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 in GABA_A-antibody encephalitis, CSF 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,⁴² basal ganglionitis in those with chorea and CRMP5/CV2-antibodies,⁸⁰ and multifocal cortical and subcortical abnormalities in patients with GABA_A-antibodies.⁸¹ In the spinal syndromes, paraneoplastic myelopathies often show a predominance for corticospinal tracts and are frequently longitudinally extensive.⁸²

Again, as with CSF studies, it is important to note that MR scan of the brain and spine can be normal in PNS. This is an especially common scenario in NMDAR-antibody encephalitis,^{46 47} in patients with amphiphysin-antibodies⁵² and in Morvan's syndrome with CASPR2-autoantibodies.⁴¹ Therefore, in a clinically and serologically appropriate setting, an unremarkable MRI should not deter from the diagnosis of some PNS. Moreover, in most cases of paraneoplastic cerebellar degeneration, initial MRI or CT is unrevealing with cerebellar atrophy visible only in later scans (figure 3).

Electrophysiology

Patients with encephalopathies will typically manifest electrophysiological abnormalities (table 3). One distinctive electroencephalogram (EEG) pattern is extreme delta brush in NMDAR-antibody encephalitis⁸³—but is usually apparent only in the profoundly encephalopathic patient, hence having limited diagnostic value.⁴⁶ An EEG study in patients with Hu-antibody showed surprisingly widespread abnormalities including in those without overt seizures or focal clinical signs.⁸⁴

Electromyography is a valuable investigation in patients with CASPR2-autoantibodies where frank neuromyotonia is common.^{41 85} Peripheral neurophysiology in PNS may delineate relevant findings as described previously, but less specific findings of sensory or sensorimotor neuropathy are also possible (table 2). In suspected LEMS, decreased compound muscle action potentials are expected; and the electrical hallmark is increment after high-frequency repetitive nerve stimulation.⁷³ Specific abnormalities consistent with bipolar cell dysfunction on electroretinogram may assist in the diagnosis of patients with melanoma-associated retinopathy antibodies.⁷⁴

OUTCOMES

Tumour identification and appropriate oncological management are key to medical and neurological stabilisation, especially as many PNS associated with cancers display a limited immunotherapy response.⁷³ 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, reports of spontaneous improvement and frequently biased interpretations of treatment benefits.⁸⁶ 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 More than one comparative observational cohort study has shown that patients with Hu-antibodies have a worse prognosis than those with CRMP5/CV2-antibodies.^{57 66}

Treatment and immunotherapy outcomes: onconeural antibodies

While many cases with onconeural antibodies are immunotherapy-resistant or only partially responsive,

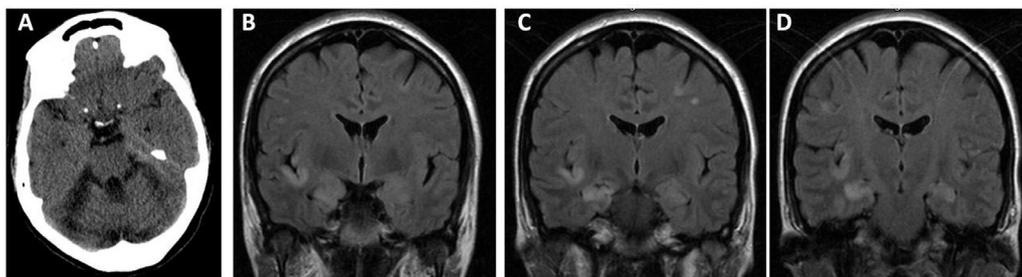


Figure 3 Central nervous system imaging in paraneoplastic encephalitides. (A) CT scan of the head showing chronic cerebellar atrophy in a patient with Yo antibodies. (B–D) FLAIR hyperintensities in a patient with AMPAR-antibody encephalitis with a thymoma. The images demonstrate multifocal inflammatory 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. AMPAR, α -amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid receptor; FLAIR, fluid-attenuated inversion recovery.

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 show some recovery with tumour removal and immunotherapy,⁴² and an immunotherapy response is also documented in CRMP5/CV2- and amphiphysin-antibody-associated neuropathies.^{65 66} Women with amphiphysin-antibody stiff-person syndrome can also make worthwhile functional gains with cancer treatment and corticosteroids.⁸⁷

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.²⁴ 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.⁸⁸ There were similarly disappointing results in a trial of intravenous immunoglobulin alone.⁸⁹ Many cases of paraneoplastic cerebellar degeneration remain refractory to treatment even if the underlying malignancy is successfully addressed, a situation which is particularly observed with Yo-antibodies.^{6 50 67} Treatment response in some of the rarer syndromes is available only in case reports.⁹⁰ The literature for treatment in paraneoplastic retinopathies is dominated by case reports, but it is generally believed that in cancer-associated retinopathy, cancer treatment alone is ineffective for visual recovery, and that additional immune treatments are beneficial.⁹¹

Treatment and immunotherapy outcomes: surface neuronal antibodies

In marked contrast, overall, the vast majority of patients with surface neuronal antibodies are immunotherapy-sensitive. In addition to oncological management, these patients merit a trial of immunotherapy, often extending to second-line or even third-line agents based on initial responses (table 2, Uy *et al*¹³). More than 80% of treated NMDAR-antibody encephalitis can be expected to have a good outcome at 24 months,⁴⁷ a figure likely to have increased since better recognition and more effective treatment protocols are commonplace. In this condition, paraneoplastic and non-paraneoplastic cases are likely to do equally well, but shorter time to oophorectomy is key in securing clinical improvement in patients with a teratoma.⁴⁶ In our experience, this benefits from close multidisciplinary discussions between radiology and gynaecology colleagues to provide a balanced approach regarding considerations around fertility preservation in young women of childbearing potential.

There is a contrasting situation for patients with CASPR2-autoantibodies, where patients with

associated thymomas show demonstrably worse outcomes compared with non-paraneoplastic patients.⁴¹ In an 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 the modified Rankin Scale score was static despite immunotherapies. However, recently in our centres, we have experienced some clinical benefits with rituximab in such patients (SR Irani and J Honnorat, unpublished data, 2021).

The syndromes associated with surface antibodies to mGluR1 and mGluR5, despite common associations with lymphoma, are typically immunotherapy responsive, and >50% of patients with mGluR5-autoantibodies can make a full recovery.^{49 58} 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.⁷³ A report of global improvement following rituximab of a patient with VGCC with LEMS and cerebellar degeneration again highlights the possible opportunities of newer therapies in recalcitrant disease

Key points

- ▶ 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 line blot/immunodot testing.
- ▶ Syndromes mediated by surface neuronal autoantibodies usually respond to prompt immunotherapy, in addition to oncological therapies; some syndromes associated with 'onconeural' antibodies may not respond, but there are important exceptions.
- ▶ There is limited high-quality trial evidence, meaning much practice is based on observational or cohort studies.

Further reading

- ▶ Graus F, Vogrig A, Muñoz-Castrillo S, *et al*. Updated diagnostic criteria for paraneoplastic neurologic syndromes. *Neurol - Neuroimmunol Neuroinflammation* 2021;8:e1014. doi:10.1212/nxi.0000000000001014
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entities.⁹² Within this group, the poorest outlook is reserved for patients with GABA_B-autoantibodies, whose functional improvement is in many cases partial and, despite immunotherapy gains, many die due to an underlying SCLC and its related complications.^{77 79}

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Competing interests SRI is a coapplicant and receives royalties on patent application WO/2010/046716 (UK patent number, 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 coapplicants 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, MedImmune, 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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