Supplemental material

Updated Diagnostic Criteria for Paraneoplastic Neurological Syndromes

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Table e-1. Novel and partially characterized antibodies.

Antibody	Neurological phenotypes	Number of patients reported	Frequency of cancer (%)	Reported tumors	Specificities
ITPR1[e74–e78]	Cerebellar syndrome, peripheral neuropathy	25	30	Breast cancer, others	
KCTD16[e3]	Limbic encephalitis	23	95	SCLC	Associate with SCLC in $GABA_BR$ LE
Neuronal intermediate filament[e79]	Cerebellar syndrome, encephalopathy	21	90	Neuroendocrine carcinomas	PNS is associated with neurofilament light chain
ANNA-3[e80]	Sensorimotor neuropathy, cerebellar syndrome	11	80	SCLC	
Adaptor protein 3B[e81]	Sensory or cerebellar ataxia	10	20	Renal carcinoma, B-cell lymphoma	
ARHGAP26[e82–e87]	Cerebellar syndrome, encephalitis/encephalopathy	10	50	Various carcinomas, B-cell lymphoma, melanoma	
Neurochondrin[e88]	Cerebellar/brainstem syndrome	8	10	Uterine carcinoma	
PDE10A[e89]	Movement disorders	7	85	Various carcinomas	
CARP VIII[e90–e92]	Cerebellar syndrome	3	100	Melanoma, ovarian & breast cancer	
Protein kinase Cγ[e93,e94]	Cerebellar syndrome	2	100	NSCLC, hepatic adenocarcinoma	
TRIM9/67[e95]	Cerebellar syndrome	2	100	NSCLC	
mGluR2[65]	Cerebellar syndrome	2	100	Small-cell tumor, rhabdomyoscarcoma	

CRMP3-4[e96]	Limbic encephalitis	1	100	Malignant thymoma
BRSK2[e97]	Limbic encephalitis	1	100	SCLC
ROCK2[e98]	Limbic encephalitis	1	100	Renal carcinoma
TRIM46[e99]	Encephalomyelitis	3	67	SCLC

Abbreviations: ANNA-3, anti-nuclear antibody 3; ARHGAP26, Rho GTPase-activating protein 26; BRSK2, BR serine/threonine kinase 2; CARP VIII, carbonic anhydrase-related protein VIII; CRMP, collapsin response-mediator protein; $GABA_BR$, gamma-aminobutyric acid-b receptor; ITPR1, inositol 1,4,5-triphosphate receptor 1; KCTD16, potassium channel tetramerization domain containing 16; mGluR2, metabotropic glutamate receptor 2; NMDAR, N-methyl-D-aspartate receptor; NSCLC, non small-cell lung cancer; PDE10A, phosphodiesterase 10A; ROCK2, Rho-associated protein kinase 2; SCLC, small-cell lung cancer; TRIM, tripartite motif-containing protein.

Table e-2. Recommendations for oncological screening in PNS according to the type of cancer suspected.

- SCLC and malignant thymoma: CT-chest ± FDG-PET/CT. For thymomas, chest MRI might be useful as well, especially in children.
- Breast cancer: mammography (breast ultrasound [US] in young women and/or dense breast) ± breast MRI. If negative, FDG-PET/CT.
- Ovarian teratoma: transvaginal US (may not be feasible in young patients) ± MRI-pelvis/abdomen. If negative, CT-chest searching for extra-pelvic teratomas. Prophylactic oophorectomy is not recommended in NMDAR encephalitis without detectable ovarian teratoma. It might be considered only in selected patients with severe neurological involvement and proven lack of response to first- and second- line immunotherapies (considering that the initial evidence of response to immunotherapy may take 2-3 months), carefully weighing the benefit/risk ratio of the procedure.
- Ovarian carcinoma: transvaginal US ± MRI-abdomen/pelvis or FDG-PET/CT. If negative, post-menopausal women with anti-Yo antibodies confirmed by two gold standard techniques and compatible neurological phenotype, should be considered for exploratory surgery or prophylactic bilateral hysterectomy and salpingo-oophorectomy.
- Testicular tumors: US ± CT of the pelvic region; MRI might be an alternative to CT, especially in children. Orchiectomy is recommended in men < 50 years old with microcalcifications on US, and confirmed Ma2 antibodies with compatible neurological phenotype. FDG-PET/CT is recommended when retroperitoneal or mediastinal germ cell tumors are suspected based on unremarkable testicular ultrasound or the detection of regressed tumors on testicular biopsy.
- Hodgkin´s lymphoma: full-body CT or FDG-PET/CT.
- Neuroblastoma: CT±MRI (CT is usually more sensitive since it identifies calcifications more easily, but MRI is preferred for staging of thoracic tumors); chest XR, abdominal US, or metabolic investigations lack of sensitivity.
- Unknown: full-body CT followed if negative by FDG-PET/CT.

Table e-3. Main differential diagnosis according to high-risk phenotypes

High-risk PNS	Differential diagnosis	Clues
EM	Meningeal carcinomatosis	Meningeal enhancement, low CSF glucose
	Neurosarcoidosis	Usually with systemic involvement that may be shown by FDG-PET
	ADEM	Anti-MOG antibodies
LE	Herpes-simplex encephalitis	Acute onset, fever, aphasia, unilateral or diffuse temporal involvement on MRI
	Human herpes virus-6 encephalitis	Usually severe, mostly in immunosuppressed patients after transplantation
	Neurosyphilis	Occasionally slowly progressive
	Whipple disease	Gastrointestinal symptoms, arthralgia, oculomasticatory myorhythmia, extratemporal lesions on MRI with variable contrast enhancement
	Autoimmune systemic diseases	Systemic signs and symptoms of SLE, Sjögren syndrome, or Behçet disease; extratemporal lesions on MRI with variable contrast enhancement
	Gliomas	Patients not fulfilling criteria for definite AE, clinical deterioration after initial improvement with steroids, unilateral (but bilateral lesions are possible), contrast enhancement
	Lymphoma	Unilateral lesions along with involvement outside the limbic system
	Status epilepticus	Reversible MRI changes
	Chronic temporal lobe epilepsy	Atrophy usually more common than hypersignal on MRI, CSF usually normal
	Wernicke´s encephalopathy	Oculomotor abnormalities, ataxia, seizures are uncommon, typical findings on MRI
Rapidly progressive cerebellar syndrome	Autoimmune cerebellar ataxia	Antibodies against gliadin and transglutaminase (gluten ataxia), GAD65, mGluR1
	Cerebellar MSA	Dysautonomia, parkinsonian features, REM sleep disturbances
	Creutzfeldt-Jakob disease	Cognitive and psychiatric symptoms, very rapid progression, typical findings on EEG and MRI
OMS	Idiopathic OMS	Younger, prodromal symptoms of viral infection/vaccination, encephalopathy less frequent
SNN	Idiopathic	Most frequent etiology, occasionally more progressive, painless, with onset at lower limbs
	Sjögren´s syndrome	Subacute or progressive, sicca syndrome symptoms, anti-SSA/SSB antibodies

	Cisplatin treatment	Usually 1 month after therapy, dose-dependent
Chronic gastrointestinal pseudo-obstruction	Associated with other diseases	Diabetes, Parkinson`s disease, scleroderma, Chagas disease
	Mechanical obstruction	Imaging studies
LEMS	Idiopathic LEMS	Patients are younger, more frequently women, non smokers, with autoimmune comorbidities and anti-SOX1 negative
	Myasthenia gravis	No dysautonomia, early involvement of ocular muscles, EMG features

Abbreviations: ADEM, acute disseminated encephalomyelitis; AE, autoimmune encephalitis; CSF, cerebrospinal fluid; EEG, electroencephalography; EM, encephalomyelitis; EMG, electromyogram; FDG-PET, Fluorodeoxyglucose positron emission tomography; GAD65, glutamic acid decarboxylase 65; LE, limbic encephalitis; HIV, human immunodeficiency virus; LEMS, Lambert-Eaton myasthenic syndrome; mGluR1, metabotropic glutamate receptor 1; MOG, myelin olygodendrocyte glycoprotein; MRI, magnetic resonance imaging; OMS, opsoclonus-myoclonus syndrome; REM, rapid eye movement; SNN, sensory neuronopathy; SLE, systemic lupus erythematosus; SPS, stiff-person syndrome; SSA, Sjögren syndrome related antigen A; SSB, Sjögren syndrome related antigen B.

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