Nora Alfugham, MD
Avi Gadoth, MD
Vanda A. Lennon, MD, PhD
Lars Komorowski, PhD
Madeleine Scharf, PhD
Shannon Hinson, PhD
Andrew McKeon, MD
Sean J. Pittock, MD

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ITPR1 AUTOIMMUNITY: FREQUENCY, NEUROLOGIC PHENOTYPE, AND CANCER ASSOCIATION

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Autoantibodies specific for the neuronal (type 1) isoform of the ubiquitously expressed inositol trisphosphate receptor (ITPR) have been reported in 8 patients to date, 5 with cerebellar ataxia (1 with breast cancer) and 3 with peripheral neuropathy (1 with lung carcinoma and 1 with multiple myeloma).[1–4] We report in this study the frequency, neurologic presentations, and oncologic associations of 14 ITPR1-immunoglobulin G (IgG)-positive patients.

Methods. The study was approved by the Mayo Clinic Institutional Review Board.

Patients. In the course of clinical service evaluation for paraneoplastic neural autoantibodies in the Mayo Clinic Neuroimmunology Laboratory (1997–2017), 117 patients were classified as having an IgG that, by mouse tissue-based indirect immunofluorescence assay (IFA), bound to the cerebellum in a "Medusa head-like" cytoplasmic staining pattern (i.e., prominently immunoreactive Purkinje cell perikaryon and dendrites) and were stored.[1,3] Clinical information was obtained by physician telephonic interview and case record review.

Serologic testing. ITPR1-specific IgG (see figure e-1 at Neurology.org/nn) was detected by transfected cell–based assay ([serum, 1:10; CSF, 1:2], Euroimmun, Germany) in 17 patients; clinical information was available in 14. Healthy control (100 adults and 45 children) and disease control subjects (30 neurologic [anti–neuronal nuclear antibody type 1 (ANNA-1/anti-Hu), Purkinje cell antibody type 1 (PCA-1/anti-Yo), PCA-2/anti-MAP1B, MS] and 60 nonneurologic [polyclonal gammopathies, Sjogren, and lupus] tested negative.

Results. The median age at neurologic symptom onset was 64 years (range 7–83 years); 10 patients were women (71%). Data available for 14 seropositive cases (table) identified 4 major neurologic manifestations: (1) peripheral neuropathy (somatic, patients 1–4; autonomic, patient 5), (2) cerebellar ataxia (patients 6–10, see figure e-1), (3) encephalitis with seizures (patients 5, 11, and 12), and (4) myelopathy (patients 2, 12, and 13).

Patient 11 had a generalized tonic-clonic seizure, and focal status epilepticus followed. EEG showed unilateral periodic discharges. After an initially favorable response to IV methylprednisolone and antiseizure medications, the dose of prednisone was tapered off. Relapse 2 weeks later required intensive care unit care. Seizures thereafter were refractory to corticosteroid, IV immunoglobulin, and antiepileptic medications. Life support was withdrawn at the family's request. Seizure and encephalopathy in patient 12 were followed 1 week later by opsoclonus myoclonus syndrome. Quadriplegia developed 3 weeks later because of myelitis. This patient's CSF was additionally positive for NMDA-R-IgG and GFAP-IgG, which may explain encephalitis and myelitis, respectively.

CSF results available in 5 patients revealed elevated protein levels and pleocytosis in 4. ITPR1-IgG titer values did not correlate with the severity or the type of clinical or oncologic phenotype. Six cancers were found in 5 patients, 1 based on PET CT and the others proven histologically (3 breast, 1 renal, and 1 endometrial). Neurologic impairment did not improve significantly in any of the 10 patients who received immunotherapy.

Frequency. Prospective detection of ITPR1-IgG in 8 patients (who were part of the 14 patients presented here) over a 12-month period represented 0.015% of 52,000 neurologic patients' specimens submitted for paraneoplastic autoantibody evaluation. By comparison, other recognized paraneoplastic antibodies' detection frequencies during that period were 0.20% for ANNA-1, 0.08% for PCA-1, 0.03% for ANNA-2 (anti-Ri), and 0.001% for PCA-Tr (delta/notch-like epidermal growth factor–related receptor).

Discussion. The neurologic manifestations encountered in patients with ITPR1 autoimmunity are more diverse than previously described. Peripheral neuropathy was as common as cerebellar ataxia and was most strongly associated with malignancy (cancer was found in 3 of 5 patients with neuropathy). In addition to its high expression in the CNS (highest in Purkinje cells of the cerebellum), ITPR1 is also expressed in the peripheral nervous system, where it is implicated in synaptogenesis and axonal growth.[5]

Table Neurologic, serologic, and oncologic characteristics of 14 ITPR1-IgG-positive patients

Patient no. -sex/age	Neurologic disorder/laboratory testing	Cancer/time of diagnosis/modality of cancer survey	ITPR1 Ab titer by IFA/coexisting Ab[a]	MRI head/spine	CSF findings	Immunotherapy	Outcome
1-M/72	Demyelinating peripheral neuropathy, sensory ataxia/EMG confirmed	Renal cell carcinoma metastatic to bones and liver/at the time of neurologic presentation/NA	Serum titer 30,720, CSF titer 512	NA	NA	PLX	No benefit/died 1 y after onset
2-F/60	Subacute, progressive axonal sensory >motor polyneuropathy/EMG confirmed also myelopathic findings with proprioceptive loss	Breast carcinoma metastatic to axillary lymph nodes/at the time of neurologic presentation/PET CT	Serum titer 122,880: AQP4/MOG-IgG negative	Spine: longitudinally extensive increased T2 signal posterior columns-tractopathy (Vitamin B12 normal); diffuse enhancement of cervical nerve roots	WCC 10/μL, Protein 78 mg/dL	IV steroids, IVIG and PLX	No benefit
3-M/54	Subacute onset of peripheral neuropathy with feet numbness/EMG confirmed	Negative/PET CT	Serum titer 960/VGKC 0.16 nM/L (LGI1 and CASPR2-IgG negative)	NA	NA	NA	NA
4-M/64	Subacute painful symmetric neuropathy/EMG confirmed diffuse axonal polyneuropathy	Negative/PET CT	Serum titer 61,440	NA	NA	Not given	NA
5-F/83	Subacute pandysautonomia (confirmed on TST and ART; EMG normal) followed 4 y later by cognitive decline encephalopathy and seizures (EEG-electrographic seizures)	Lung mass with mediastinal lymphadenopathy. FDG avid mass, left scapula/at the time of neurologic presentation/PET CT	Serum titer 30,720, CSF titer 128	Generalized brain atrophy, prominent in temporal lobes	Protein 56 mg/dL	Steroids	Good initially but later progressed
6-F/71	Acute onset vertigo, dysphasia, agraphia followed by cerebellar ataxia	Negative/PET CT, mammogram, cervical dysplasia reported on PAP smear	Serum titer 245,760, CSF titer 8,192, GAD65-IgG 0.37 nM/L	MRI head: cerebellar atrophy	Normal	Steroid, IVIG, and PLX	No benefit WC at 5-y follow-up
7-F/33	Subacute cerebellar ataxia, nystagmus, vertigo, and nausea	Negative/PET CT, mammogram	CSF titer 256 (no serum available)	Normal MRI. PET CT: increased uptake in the right cerebellum	Elevated WBC, protein 120 mg/dL	Steroid and PLX	Minimal benefit/died on follow-up
8-F/7	Subacute onset cerebellar ataxia (truncal and appendicular), double vision, dysarthria and myoclonus: preceeding viral illness	Negative/PET CT	CSF titer 64 (CSF, no serum available)	Cerebellar signal change with patchy T2 hyperintense signal change and some patchy enhancement after contrast administration. Later MRI: cerebellar atrophy figure e-1	WBC, 42/μl (81% lymph) protein 49 mg/dL, OCB+	Steroid, IVIG, and PLX	Minimal benefit
9-F/65	Subacute hearing loss in both ears, double vision, ataxia, and weakness in extremities	Breast carcinoma, with malignant cells in CSF/at the time of neurologic presentation/mamogram	Serum titer 7,680	Normal	Cytology + malignant cells	Not given	Dead at last follow-up
10-F/64	Vertigo, ataxia, and visual blurring, severe weight loss	Negative	Serum titer 61,440	NA	NA	Not given	Dead at last follow-up
11-F/83	Acute status epilepticus	Negative/PET CT	Serum titer 61,440	Subcortical right occipito-parietal high T2 signal with contrast enhancement	NA	IV steroids, IVIG,	Dead at last follow-up
12-M/21	Subacute seizure and encephalopathy, followed by opsoclonus myoclonus then extensive myelitis, preceeding viral illness	Negative/PET CT, testicular US and bone marrow biopsy	CSF titer 8 (NMDA-R, GFAP), AQP4/MOG-IgG negative in serum	R mesial temporal lobe and right Rt middle cerebellar peduncle T2 signal changes. Later MRI: long myelitis and lumbar nerve root enhancement	Yes/WBC 188 leukocytes/μL, protein 127 mg/dL	Steroid, IVIG, RTX, PLX	Quadriplegic, ICU >4 mo

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Table Continued

Patient no. -sex/age	Neurologic disorder/laboratory testing	Cancer/time of diagnosis/modality of cancer survey	ITPR1 Ab titer by IFA/coexisting Ab[a]	MRI head/spine	CSF findings	Immunotherapy	Outcome
13-F/13	Subacute rapidly progressive spastic paraparesis	No: history of Fanconi anemia, 5 years after bone marrow transplantation	CSF titer >8, serum titer >240	Brain MRI has shown CNS calcifications since birth; however, they may possibly be progressive. Developed 3 enhancing lesions in the CNS with involvement of the spinal cord, cerebellum, meninges, and supratentorially	NA	IVIG, PLX, and RTX	Short lasting mild benefit
14-F/65	Cervical dystonia, insomnia, anxiety and depression	Breast and endometrial carcinomas/ before neurologic presentation/PET CT	Serum titer 960	NA	NA	IVIG	No benefit

Abbreviations: AMPA-R = α-amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid receptor; AQP4 = Aquaporin-4; ART = autonomic reflex test; CBA = Cell-based assay; DNER = delta/notch-like epidermal growth factor–related receptor; FDG = Fludeoxyglucose; GABAB-R = gamma-aminobutyric acid B receptor; GFAP = Glial fibrillary acidic protein; ICU = intensive care unit; IFA = immunofluorescence assay; IgG = immunoglobulin G; ITPR = inositol trisphosphate receptor; IVIG = IV immunoglobulin; MOG = Myelin oligodendrocyte glycoprotein; NA = not available; PLX = plasmapheresis; RTX = Rituximab; TST = thermoregulatory sweat test; US = ultrasound; WBC = white blood cell; WC = wheelchair; WCC = white cell count.

[a] All specimens were submitted for comprehensive paraneoplastic neural autoantibody evaluation, which includes testing for cation channel antibodies (voltage-gated calcium channels [P/Q-type and N-type], voltage-gated potassium channels [VGKCs, including LGI1 and CASPR2] and nicotinic acetylcholine receptors [nAChRs, muscle-type and ganglionic-type]), skeletal muscle striational antibodies, antineuronal nuclear autoantibodies (ANNAs), types 1 (anti-Hu), 2 (anti-Ri), and 3; Purkinje cell cytoplasmic autoantibodies (PCAs), types 1 (anti-Yo), 2, and Tr (DNER); antiglial/neuronal nuclear antibody type 1 (AGNA-1 and SOX 1); collapsin response-mediator protein-5 (CRMP-5 and CV2) IgG; amphiphysin IgG; glutamic acid decarboxylase (GAD65), NMDA-R, GABAB-R, and AMPA-R antibodies.

The wide dissemination of cancer (including metastases to bone or liver) observed in ITPR1-IgG–positive patients contrasts with the limited stage cancers (usually restricted to regional lymph nodes) encountered in paraneoplastic neurologic autoimmunity related to small cell lung carcinomas.[6] ITPR1 may be a biomarker of more aggressive tumor behavior, since ITPR1 is implicated in cell migration, and other ITPR isoforms in cancer dissemination. One study reported that resistance to conventional anticancer treatment in patients with renal cell carcinoma related to von Hippel-Lindau syndrome is associated with ITPR1 upregulation in the tumor, which protects against natural killer cell cytotoxicity through induction of autophagy.[7] Other ITPR isoforms have been implicated in tumor growth promotion. Our data mandate a thorough search for cancer when ITPR1-IgG is detected, given the 36% frequency of malignancy we report. This estimate may be low because clinical information and follow-up for some patients were limited. The introduction of assays to detect ITPR1-IgG as part of service paraneoplastic neural antibody testing will allow for better definition of the full clinical and oncologic spectrum.

From the Department of Laboratory Medicine and Pathology (N.A., A.G., V.A.L., S.H., A.M., S.J.P.), Department of Neurology (V.A. L., A.M., S.J.P.), and Department of Immunology (V.A.L.), Mayo Clinic, Rochester, MN; and Institute for Experimental Immunology (L.K., M.S.), Affiliated to Euroimmun AG, Luebeck, Germany.

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Disclosure: N. Alfugham and A. Gadoth report no disclosures. V.A. Lennon holds a patent for and receives royalties from RSR/Kronus for sale of aquaporin-4 autoantibody testing kits and for commercial aquaporin-4 autoantibody testing performed outside Mayo Clinic; received research support from the NIH; has a patent pending for GFAP and MAP1B as markers of neurological autoimmunity and paraneoplastic disorders; has a potential financial interest in the technology "Aquaporin-4 as an aid for cancer diagnosis"; and receives license fee payments for Non-Mayo sites performing "home brew" diagnostic testing for aquaporin-4 autoantibody. L. Komorowski is employed by Euroimmun AG, a company that develops, produces, and manufactures immunoassays for the detection of disease-associated antibodies. M. Scharf is an employee of the Euroimmun AG, a company that develops, produces, and manufactures immunoassays for the detection of disease-associated antibodies and holds a patent for diagnostic test for the detection of autoantibodies against ITPR1. S. Hinson reports no disclosures. A. McKeon has a patent pending for GFAP and MAP1B as markers of neurological autoimmunity and paraneoplastic disorders; consulted for Grifols, MedImmune, and Euroimmun; and received research support from MedImmune and Euroimmun but has not received personal compensation. S.J. Pittock holds patents that relate to functional AQP4/NMO-IgG assays and NMO-IgG as a cancer marker; has a patent

pending for GFAP and MAP1B as markers of neurological autoimmunity and paraneoplastic disorders; consulted for Alexion, Grifols, Euroimmun, and MedImmune; and received research support from Euroimmun, Grifols, MedImmune, and Alexion, RO1 NS065829-01. All compensation for consulting activities is paid directly to Mayo Clinic. Go to Neurology.org/nn for full disclosure forms. The Article Processing Charge was funded by Department of Laboratory Medicine and Pathology, Mayo Clinic.

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Correspondence to Dr. Pittock: pittock.sean@mayo.edu

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ITPR1 autoimmunity: Frequency, neurologic phenotype, and cancer association

Nora Alfugham, Avi Gadoth, Vanda A. Lennon, et al.

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