ITPR1 AUTOIMMUNITY: FREQUENCY, NEUROLOGIC PHENOTYPE, AND CANCER ASSOCIATION

Autoantibodies specific for the neuronal (type 1) isoform of the ubiquitously expressed inositol triphosphate 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

Notes

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| Patient no. -sex/age | Neurologic disorder/laboratory testing | Cancer/time of diagnosis/modality of cancer survey | ITPR1 Ab titer by IFA/coexisting Ab* | 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 0.15 nM/L (LG1 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 | Serum 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 | Serum 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/namogram | 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 B [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 |

Continued
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. 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. 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.

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