Aquaporin-4 Autoantibodies in a Paraneoplastic Context

Sean J. Pittock, MD; Vanda A. Lennon, MD, PhD

Background: The neuromyelitis optica IgG autoantibody (NMO-IgG) is a validated biomarker for NMO and an emerging spectrum of inflammatory central nervous system–demyelinating disorders. Its antigen is the astrocytic water channel aquaporin-4; NMO-IgG has not been described in a cancer context.

Objectives: To report (1) neurologic and oncologic correlates for patients incidentally identified as NMO-IgG seropositive in a blinded evaluation for paraneoplastic autoantibodies and (2) the frequency of cancer in NMO-IgG–seropositive patients.

Design: Observational, retrospective case series.

Setting: Neuroimmunology Laboratory and Neurology Clinical Practice, Mayo Clinic College of Medicine.

Patients and Methods: From 1998 to 2007, we detected NMO-IgG in 2 patient groups: (1) 31 patients (88% female) identified incidentally among 180,000 patients evaluated for paraneoplastic autoantibodies and (2) 141 patients identified through physician-requested serological evaluation for a suspected NMO-spectrum disorder.

Results: In the first group, clinical information was available for 28 patients (90%). An NMO-spectrum disorder was diagnosed in 26 patients (93%), of whom 6 had a neoplasm (5 carcinomas [2 breast, 1 lung, 1 thymic, and 1 uterine cervical] and 1 B-cell lymphoma) and 1 had monoclonal gammopathy. In 4 patients, NMO-related symptoms followed neoplasia detection (median, 14 [range 3-18] months), and in 2 patients, symptoms preceded neoplasia detection (by 5 and 3 months). Two patients had carcinoma (1 breast and 1 lung) without neurologic evidence of an NMO-spectrum disorder. In the second group, neoplasms were recorded in 7 seropositive patients (5.0%) with a clinically diagnosed NMO-spectrum disorder: 3 carcinomas (all breast), 1 thyroid Hurthle cell, 1 carcinoid, 1 pituitary somatotropinoma, and 1 B-cell lymphoma. An eighth patient had monoclonal gammopathy.

Conclusions: Aquaporin-4–specific IgG in some cases of NMO may reflect a paraneoplastic immune response. The clinical utility of this autoantibody as a cancer marker warrants prospective investigation.

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METHODS

The study was approved by our institutional review board. We describe 2 groups of patients identified serologically as NMO-IgG positive in the Mayo Clinic’s Neuroimmunology Laboratory during a 10-year period.

GROUP 1

Among approximately 180,000 patients whose serum samples were tested prospectively for paraneoplastic autoantibodies on a service basis, the indirect immunofluorescence screening component (on a composite substrate of mouse tissues) identified 31 patients identified incidentally as NMO-IgG positive. In group 1, clinical information was available for 28 of 31 patients identified incidentally as NMO-IgG seropositive: 13 were evaluated at the Mayo Clinic; 26 (93%) were women and 8 (28%) were black. Neurological symptoms and signs in 26 patients (93%) fit the recognized spectrum of NMO: 8 fulfilled 2006 diagnostic criteria for NMO, 6 had recurrent/relapsing longitudinally extensive transverse myelitis, 9 had a single episode of longitudinally extensive transverse myelitis, and 3 had relapsing optic neuritis. Seven of these 26 patients (27%) had an associated neoplasm (Table 1); NMO-related symptoms followed the diagnosis of cancer in 5 of those patients (median, 14 [range 3-18] months) and preceded the diagnosis of cancer in 2 (by 5 and 3 months).

GROUP 2

At the physician’s request, 141 seropositive patients were evaluated for NMO-IgG, because the clinical presentation was consistent with an NMO-spectrum disorder. Information for these Mayo Clinic patients was obtained by review of their medical records.

SEROLOGIC TESTING

All serum samples were titrated in doubling dilutions to ascertain the endpoint dilution yielding positive immunofluorescence staining. Where serum was available (Table 1 and Table 2), IgG specific for aquaporin-4 was confirmed by quantitative green fluorescent protein-linked aquaporin-4 immunoprecipitation assay in all patients identified with cancer.

Table 1. Clinical Characteristics of Patients in Group 1 With Proven Cancer (n = 8) or Monoclonal Gammopathy (n = 1)a

<table>
<thead>
<tr>
<th>Patient No.</th>
<th>Sex</th>
<th>Race/Ethnicity</th>
<th>NMO-IgG Titer</th>
<th>Neurological Diagnosis</th>
<th>Age at Onset of Neurological Disorder, y</th>
<th>Most Recent Neoplasm</th>
<th>Time From Diagnosis of NMO or LETM to Cancer Diagnosis, mob</th>
</tr>
</thead>
<tbody>
<tr>
<td>1/F,c,d</td>
<td>Black</td>
<td>1920a</td>
<td>Cerebral metastasis</td>
<td>55</td>
<td>Breast carcinoma</td>
<td>NA</td>
<td>uint time unknown</td>
</tr>
<tr>
<td>2/F</td>
<td>Black, Arab</td>
<td>1920</td>
<td>NMO</td>
<td>36</td>
<td>Breast carcinoma (metastasis)</td>
<td>5</td>
<td></td>
</tr>
<tr>
<td>3/F</td>
<td>White</td>
<td>15 360a</td>
<td>LETM</td>
<td>63</td>
<td>Breast carcinoma (infiltrating ductal)</td>
<td>14</td>
<td></td>
</tr>
<tr>
<td>4/F,c</td>
<td>White</td>
<td>7680</td>
<td>Cerebral metastasis</td>
<td>63</td>
<td>Lung carcinoma</td>
<td>NA</td>
<td>uint time unknown</td>
</tr>
<tr>
<td>5/F</td>
<td>Black</td>
<td>30 720</td>
<td>LETM</td>
<td>66</td>
<td>Lung carcinoma</td>
<td>Anteceded rLETM (interval unknown)</td>
<td></td>
</tr>
<tr>
<td>6/F</td>
<td>Black</td>
<td>7680a</td>
<td>NMO</td>
<td>44</td>
<td>Thymic carcinoma</td>
<td>3</td>
<td></td>
</tr>
<tr>
<td>7/F</td>
<td>Black</td>
<td>15 360</td>
<td>rLETM</td>
<td>18</td>
<td>Cervical carcinoma</td>
<td>3</td>
<td></td>
</tr>
<tr>
<td>8/M</td>
<td>White</td>
<td>15 360</td>
<td>rLETM</td>
<td>70</td>
<td>Seminoma (metastasis)</td>
<td>288</td>
<td></td>
</tr>
<tr>
<td>9/F</td>
<td>Black</td>
<td>30 720</td>
<td>rLETM</td>
<td>61</td>
<td>Monoclonal gammopathy</td>
<td>Anteceded rLETM (interval unknown)</td>
<td></td>
</tr>
</tbody>
</table>

Abbreviations: LETM, longitudinally extensive myelitis; NA, not applicable; NMO, neuromyelitis optica; rLETM, recurrent longitudinally extensive myelitis.

a Indicates NMO-IgG was detected incidentally in the immunofluorescence screening component of service paraneoplastic evaluation of 180,000 patients. All 6 patients tested were confirmed positive for aquaporin-4 IgG by quantitative immunoprecipitation assay (patient 3, 671 pmol/L; patient 4, 57 pmol/L; patient 5, 1990 pmol/L; patient 6, 611 pmol/L; patient 7, 341 pmol/L; and patient 9, 31 pmol/L [normal < 5.0 pmol/L]). Serum samples were unavailable for testing by immunoprecipitation assay in the remaining 3 patients (patients 1, 2, and 8). It was not proven that patient 9 had a B-cell neoplasm.
b Negative value indicates cancer was diagnosed first.
c Patient lacked evidence of NMO or LETM.
d Patient had a headache and diplopia due to hydrocephalus; symptoms resolved following the implantation of a ventriculoperitoneal shunt.
e Cerebrospinal fluid was also NMO-IgG positive.
comment

This article highlights the specificity of NMO-IgG for a recently recognized spectrum of inflammatory CNS-dememyelinating disorders. Among 180,000 patients evaluated in 10 years on a service basis for paraneoplastic autoantibodies, 93% of the 0.02% found incidentally to have NMO-IgG had a CNS disorder consistent with the NMO spectrum. Of those whose clinical picture was consistent with CNS aquaporin-4 autoimmunity, 27% had a recent cancer diagnosis. Most remarkable was the finding of cancer in 10 years on a service basis for paraneoplastic autoimmune disease, specific for the collagen-response mediator protein 5 (CRMP-5), is expressed in neurons and oligodendrocytes in the adult nervous system. The second, the nuclear transcription factor SOX1, is expressed in progenitors of neurons and astrocytes in adult brain. Collapsin-response mediator protein 5–IgG reflects an immune response initiated by small cell lung carcinoma or thymoma. The neurological presentation is multifocal in most CRMP-5–IgG–positive patients, but some patients present with a syndrome of myelopathy and optic neuropathy that mimics NMO. Its imaging and histopathologic findings are distinct from NMO; SOX1-IgG (the anti-glial nuclear antibody/anti-neuronal nuclear antibody type 4 [AGNA/ANNA-4]) is also a marker of immune responses initiated by small cell lung carcinoma antigens.

Aquaporin-4 is the most abundant water channel in the CNS. It is mercurial insensitive and highly expressed in the astrocytic end-feet at the glia limits of the blood-brain barriers. Synapses and paranodes of myelinated axons. Outside the CNS, aquaporin-4 is expressed in membranes of skeletal muscle, glandular epithelia (breast and salivary glands), the lungs (tracheal and bronchial epithelium), kidneys (basolateral membranes of distal collecting tubules), stomach (papillae cells), and colon (epithelium). Tissue microarray analyses have revealed aquaporin-4 immunoreactivity in 11 of the 11 tested cancer types encountered in this study. This observation supports our hypothesis that aquaporin-4 may be pertinent clinically as a tumor antigen. Biological properties recently assigned to aquaporins are essential determinants of tumor cell extravasation and metastatic potential.

Table 2. Clinical Characteristics of Patients in Group 2 With Proven Cancer (n = 7) or Monoclonal Gammopathy (n = 1)∗

<table>
<thead>
<tr>
<th>Patient No./ Sex</th>
<th>Race/ Ethnicity</th>
<th>NMO-IgG Titer</th>
<th>Neurological Diagnosis</th>
<th>Age at Onset of Neurological Disorder, y</th>
<th>Most Recent Neoplasm</th>
<th>Time From Diagnosis of NMO to Cancer Diagnosis, mo*</th>
</tr>
</thead>
<tbody>
<tr>
<td>1/F 2/F 3/F 4/F 5/F 6/F 7/F 8/M</td>
<td>Black White White Argentinean White White Filipino Black</td>
<td>7680 120 120 480 1920 1920 15 360 7680</td>
<td>rLETM NMO NMO NMO NMO NMO</td>
<td>49 55 53 51 31 51 47 40</td>
<td>Breast carcinoma Breast carcinoma Thyroid (Hürthle cell) Carcinoid tumor Pituitary somatotropinoma Breast carcinoma B-cell lymphoma Monoclonal gammopathy</td>
<td>– 6 60 – 12 96 – 3 180 55 11</td>
</tr>
</tbody>
</table>

Abbreviations: LETM, longitudinally extensive myelitis; NMO, neuromyelitis optica; rLETM, recurrent longitudinally extensive myelitis.

*Identified among 141 seropositive patients at the Mayo Clinic who were tested for NMO-IgG because the clinical presentation was suspected to be an NMO-spectrum disorder. All 5 patients tested were confirmed positive for aquaporin-4–IgG by quantitative immunoprecipitation assay (patient 1, 40 pmol/L; patient 2, 20 pmol/L; patient 3, 15 pmol/L; patient 4, 26 pmol/L; and patient 7, 12.4 pmol/L [normal < 5.0 pmol/L]). Serum samples were unavailable for testing by immunoprecipitation assay in the remaining 3 patients (patients 5, 6, and 8).

†Negative value indicates cancer was diagnosed first.

‡Received azathioprine.
tial. These include enablement of cell migration (by facilitating transmembrane water influx into lamellipodia [dynamic cellular protrusions at the leading edge of migrating cells]) and adhesion properties conferred by an alternatively spliced isoform of aquaporin-4 (lacking N-terminal residues 1-22). It remains to be determined whether aquaporin-4 autoimmunity protects against tumor spread.

The pathogenicity we propose for NMO-IgG is analogous to that demonstrated for the muscle acetylcholine-receptor antibody, which causes myasthenia gravis by impairing neuromuscular transmission. The acetylcholine-receptor antibody is a clinically useful marker for myasthenia gravis as well as for thymoma in patients without myasthenia gravis. Furthermore, we recognize acetylcholine-receptor antibodies in patients with cancer (small cell lung cancer or thymoma) and other paraneoplastic autoantibodies (eg, ANNA-1, 5%; CRMP-5-IgG, 8%) in patients who lack any clinical or electrophysiologic signs of myasthenia gravis. Prospective studies are needed to investigate the frequency of aquaporin-4 autoantibodies in patients with cancer and the protein and messenger RNA expression in neoplasms derived from seropositive patients.

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Correspondence: Vanda A. Lennon, MD, PhD, Neuroimmunology Laboratory, Hilton 3-79, Mayo Clinic, 200 First St SW, Rochester, MN 55905 (lennon.vanda@mayo.edu).

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Financial Disclosure: The authors disclose that, in accordance with the Bayh-Dole Act of 1980 and Mayo Foundation policy, Dr Lennon stands to receive royalties for the discovery related to the aquaporin-4 autoantigen. To date, Dr Lennon has received a total of less than $1000 in royalties. Drs Pittcock and Lennon are named inventors on a patent application filed by the Mayo Foundation for medical education and research that relates to the NMO (aquaporin-4) antibody and its application to cancer.

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REFERENCES