

# Aquaporin-4 Autoantibodies in a Paraneoplastic Context

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**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 neurological 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 Hürthle 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.

*Arch Neurol.* 2008;65(5):629–632

**N**EUROMYELITIS OPTICA IGG (NMO-IgG) is a sensitive and specific biomarker for inflammatory central nervous system (CNS)–demyelinating disorders collectively recognized as NMO-spectrum disorders (NMO, relapsing optic neuritis, and relapsing longitudinally extensive transverse myelitis).<sup>1</sup> These disorders are often misdiagnosed as multiple sclerosis.<sup>1</sup> Unlike patients with multiple sclerosis, patients with NMO-spectrum disorders frequently have clinical and serological stigmata of autoimmunity.<sup>2</sup> To date, NMO-IgG has been reported only in patients with clinical evidence of an NMO-spectrum disorder.

The antigen of NMO-IgG is the astrocytic water channel aquaporin-4. Central nervous system lesions typical of aquaporin-4 autoimmunity with or without myelin loss are inflammatory with focal deposits of immunoglobulin and activated complement products and vasculocen-

tric loss of aquaporin-4 in regions of astrocytic endfeet.<sup>1</sup> The immunopathologic findings and reported benefit of plasmapheresis<sup>3,4</sup> and monoclonal anti-CD20 B-cell antibody (rituximab) therapy<sup>5</sup> support recent data demonstrating a role for complement-activating aquaporin-4–specific IgG as an initiator of the CNS-restricted accompaniments of NMO-IgG.<sup>6</sup> We recently reported detection of NMO-IgG in a patient who presented with NMO in the setting of thymic carcinoma.<sup>7</sup> That case and additional cases of cancer-associated NMO identified fortuitously in the course of paraneoplastic autoantibody evaluation in Mayo Clinic's Neuroimmunology Laboratory suggest the existence of a paraneoplastic subgroup of patients with NMO.

The data we present suggest that aquaporin-4 autoimmunity may, in some patients, reflect a tumor-initiated immune response. We report clinical and oncologic associations for 28 of 31 patients in whom NMO-IgG was detected incidentally in the

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

Patient No./Sex	Race/Ethnicity	NMO-IgG Titer	Neurological Diagnosis	Age at Onset of Neurological Disorder, y	Most Recent Neoplasm	Time From Diagnosis of NMO or LETM to Cancer Diagnosis, mo <sup>b</sup>
1/F <sup>c,d</sup>	Black	1920 <sup>e</sup>	Cerebral metastasis	55	Breast carcinoma	NA
2/F	Black, Arab	1920	NMO	36	Breast carcinoma (metastasis)	5
3/F	White	15 360 <sup>e</sup>	LETM	63	Breast carcinoma (infiltrating ductal)	- 14
4/F <sup>c</sup>	White	7680	Cerebral metastasis	63	Lung carcinoma	NA
5/F	Black	30 720	LETM	66	Lung carcinoma	Anteceded rLETM (interval unknown)
6/F	Black	7680 <sup>e</sup>	NMO	44	Thymic carcinoma	- 3
7/F	Black	15 360	rLETM	18	Cervical carcinoma	3
8/M	White	15 360	rLETM	70	Seminoma (metastasis)	- 288
					Bladder carcinoma	- 140
					B-cell lymphoma	- 18
9/F	Black	30 720	rLETM	61	Monoclonal gammopathy	Anteceded rLETM (interval unknown)

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

<sup>a</sup>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.

<sup>b</sup>Negative value indicates cancer was diagnosed first.

<sup>c</sup>Patient lacked evidence of NMO or LETM.

<sup>d</sup>Patient had a headache and diplopia due to hydrocephalus; symptoms resolved following the implantation of a ventriculoperitoneal shunt.

<sup>e</sup>Cerebrospinal fluid was also NMO-IgG positive.

course of paraneoplastic serological evaluation. The neurological presentations (93% consistent with an NMO-spectrum disorder) confirmed the high specificity of NMO-IgG for inflammatory CNS-demyelinating disorders of this type. The frequency of cancer in patients whose neurological presentations were consistent with an NMO-spectrum disorder was 31% (compared with 5.0% among NMO-IgG-seropositive patients presenting to the Mayo Clinic's Neurology Department with an NMO-spectrum disorder). Most remarkably, all 7% of the incidentally identified seropositive patients without evidence of an NMO-spectrum disorder had recent diagnoses of cancer.

## 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 serum samples with IgG yielding a staining pattern consistent with NMO-IgG. In no case had the ordering physician initially entertained a diagnosis of NMO. Clinical information was available for 16 of the 18 patients evaluated outside the Mayo Clinic by review of case records provided by outside physicians, physician telephone interviews, and physician-provided responses to form questionnaires.

### 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.<sup>1</sup> 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.<sup>8,9</sup>

## RESULTS

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).

**Table 2. Clinical Characteristics of Patients in Group 2 With Proven Cancer (n = 7) or Monoclonal Gammopathy (n = 1)<sup>a</sup>**

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

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

<sup>a</sup>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).

<sup>b</sup>Negative value indicates cancer was diagnosed first.

<sup>c</sup>Received azathioprine.

The remaining 2 patients in group 1 (7%; patients 1 and 4) (Table 1) lacked symptoms and signs consistent with the currently recognized spectrum of NMO. Both had carcinoma (1 lung and 1 breast), with neurological symptoms attributable to brain metastases (magnetic resonance imaging results were compatible in both and spinal fluid cytology was positive in patient 1).

In group 2, 7 of 141 patients (5.0%) had a history of neoplasm (Table 2): 3 carcinomas (all breast), 1 thyroid Hürthle cell, 1 carcinoid, 1 pituitary somatotropinoma, and 1 B-cell lymphoma. An eighth patient had monoclonal gammopathy (Table 2).

## COMMENT

This article highlights the specificity of NMO-IgG for a recently recognized spectrum of inflammatory CNS-demyelinating disorders.<sup>1</sup> 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 carcinoma (breast in 1 and lung in 1) in 2 seropositive patients who lacked clinical evidence of an inflammatory CNS-demyelinating disorder. The findings in these patients suggest that, in some cases, aquaporin-4-specific IgG may be produced in the course of a tumor immune response.

Thymoma and thymic carcinoma have previously been reported as sporadic accompaniments of NMO.<sup>7,10</sup> Our documentation of 9 patients (7 with an NMO-spectrum disorder) in whom NMO-IgG was associated temporally with cancer justifies consideration of an underlying neoplasm in NMO-IgG-seropositive patients presenting with transverse myelitis or optic neuritis. For 3 of those 9 patients (33%), breast carcinoma was the most recently identified neoplasm. The detection of NMO-IgG in 2 patients whose neurological symptoms were attributable to CNS metastases of breast and lung carcinomas supports our suggestion that neoplastic cells may

provide the antigen initiating an aquaporin-4 immune response.

Tumor cells express, as onconeural antigens, proteins that are normally expressed by mature neurons, glia, or muscle. Cancer-directed immune responses initiated by those antigens have the potential to target autoantigens in the nervous system.<sup>11-14</sup> Aquaporin-4-IgG is the third glial-reactive IgG autoantibody recognized in a paraneoplastic context. The first glial antigen reactive with IgG autoantibody, specific for the collapsin-response mediator protein 5 (CRMP-5), is expressed in neurons and oligodendrocytes in the adult nervous system.<sup>14,15</sup> The second, the nuclear transcription factor SOX1, is expressed in progenitors of neurons and astrocytes in adult brain.<sup>16</sup> 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.<sup>14</sup> Its imaging and histopathologic findings are distinct from NMO<sup>17,18</sup>; SOX1-IgG<sup>19,20</sup> (the anti-glial nuclear antibody/anti-neuronal nuclear antibody type 4 [AGNA/ANNA-4]<sup>21,22</sup>) 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<sup>23</sup> and highly expressed in the astrocytic end-feet at the glia limitans of the blood-brain barriers,<sup>1,8,23</sup> synapses,<sup>23</sup> and paranodes<sup>6</sup> of myelinated axons.<sup>5</sup> 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 (parietal cells), and colon (epithelium).<sup>24,25</sup>

Tissue microarray analyses have revealed aquaporin-4 immunoreactivity in 11 of the 11 tested cancer types<sup>26</sup> 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 poten-

tial. These include enablement of cell migration (by facilitating transmembrane water influx into lamellipodia [dynamic cellular protrusions at the leading edge of migrating cells])<sup>27,28</sup> and adhesion properties conferred by an alternatively spliced isoform of aquaporin-4 (lacking N-terminal residues 1-22).<sup>29</sup> 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.<sup>30</sup> 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)<sup>31</sup> and other paraneoplastic autoantibodies (eg, ANNA-1, 5%; CRMP-5-IgG, 8%)<sup>32</sup> 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.

Accepted for Publication: November 15, 2007.

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Author Contributions: Study concept and design: Pittock and Lennon. Acquisition of data: Pittock and Lennon. Analysis and interpretation of data: Pittock and Lennon. Drafting of the manuscript: Pittock. Critical revision of the manuscript for important intellectual content: Pittock and Lennon. Obtained funding: Lennon. Administrative, technical, and material support: Pittock and Lennon. Study supervision: Pittock and Lennon.

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 Pittock 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.

Funding/Support: This study was supported by the Mayo Foundation (Drs Pittock and Lennon) and the Ralph Wilson Medical Research Foundation (Dr Lennon).

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