AQUAPORIN-4 IGG AUTOIMMUNE SYNDROME AND IMMUNOREACTIVITY ASSOCIATED WITH THYROID CANCER

Tumor cells can express so-called onconeural antigens, which are normally restricted to mature neurons and glial cells in the CNS.1 The detection of neural-reactive immunoglobulin G (IgG) aids the diagnosis of paraneoplastic neurologic syndromes (PNS);2 however, the diagnostic utility and potential pathogenicity of autoantibodies vary between neurologic diseases. By contrast, anti-aquaporin-4 (AQP4) IgG from patients with neuromyelitis optica spectrum disorder (NMOSD) is a specific biomarker for NMOSD.2,3 AQP4 is the most abundant water channel in the CNS, particularly abundant on astrocytes, forming the glia limitans of the blood–brain barrier.3 There is compelling evidence that AQP4-IgG reactivity and pathogenicity is restricted to the CNS, probably through an impaired blood–brain barrier.2,3 The clinical features of NMOSD include inflammation of the optic nerve, spinal cord, and specific brain areas coinciding with sites of high AQP4 expression.2,3 Some cases of NMOSD thus far reported may reflect a paraneoplastic immune response.4

Case report. In 2002, a 64-year-old man with no history of CNS diseases developed sudden bilateral vision loss and constricted visual fields. Visual acuity was 1/36 and 6/24 in the right and left eye, respectively. Bilateral optic disc edema, greater in the right eye, was noted. Intraocular and intracranial pressures were normal. The neurologic examination, brain MRI, and CSF were normal except for the presence of oligoclonal bands in CSF. He did not receive any treatment. After 3 months, atrophy of the optic head and visual loss (2/36) of the right eye was apparent; the left eye was normal. AQP4-IgG was not determined at disease onset. Two years before the onset of optic neuritis, the patient had undergone surgical thyroidectomy and radioactive iodine ablation for an aggressive oncocytic cancer of the thyroid (follicular type). No evidence of metastatic disease was detected by whole-body MRI. The patient was negative for serum antithyroglobulin antibodies and antithyroid peroxidase antibodies.

In 2006, recurrent dyspepsia occurred. A gastroscopy demonstrated an ulcerating jejunal tumor, which was surgically removed and diagnosed as adenocarcinoma. Serum AQP4-IgG, anti-Ma2/TA, antitransglutaminase, and antinuclear antibodies were detectable in 2010. Brain MRI was normal and whole-body MRI remained negative for metastatic disease. Three years later (2013), the patient died of disseminated adenocarcinoma in the retroperitoneum, lymph nodes, and gastrointestinal tract. No autopsy was performed. Potentially deleterious germline mutations such as RET, TP53, and the mismatch repair genes MLH1, MSH2, MSH6, and PMS2 were investigated, but none was identified. Immunohistochemical staining for AQP4 in the paraffin-embedded neoplastic thyroid tissue revealed high-level expression of AQP4 in multifocal areas (figure). There was no AQP4 expression in the neoplastic tissue from the jejunum (not shown).

Discussion. We report the clinical and laboratory investigations of a patient with NMOSD who developed 2 apparently unrelated malignancies over a 6-year period. AQP4 was expressed in thyroid neoplastic tissue and later AQP4-IgG was detectable in serum. These findings suggest that autoimmunity against tumor-expressed AQP4 potentially elicited development of NMOSD, extending the spectrum of paraneoplastic AQP4 autoimmunity.4 Reportedly, 5% of patients with AQP4-IgG seropositive NMOSD had a history of neoplastic disease.5 Furthermore, 27% of individuals undergoing investigation for PNS were found to have detectable AQP4-IgG.4 Congruent with the current case, high AQP4 antigen expression in neoplastic tumor cells has been demonstrated in PNS.5 Outside the CNS, AQP4 is normally expressed at low levels in basolateral plasma membranes of epithelia in a number of tissues.6 It has been suggested that the differential expression of AQP4 may reflect the biological nature of neoplastic thyroid cells.6 In this case, the thyroid tumor was characterized as oncocytic carcinoma with high

Kerstin Soelberg, MD
Stine R. Larsen, MD
Marlene T. Moerch, MSc
Mads Thomassen, PhD
Klaus Brusgaard, PhD
Friedemann Paul, MD
Klaus Brusgaard, PhD
Mads Thomassen, PhD
Marlene T. Moerch, MSc
Stine R. Larsen, MD
Kerstin Soelberg, MD

Neurol Neuroimmunol Neuroinflamm 2016;3:e252; doi: 10.1212/NNX.0000000000000252
expression of AQP4, which appeared in a multifocal pattern (figure).

In addition to serum AQP4 IgG positivity, anti-Ma2/TA was also detected. This antibody is viewed as an indicator of limbic encephalitis, of which the patient did not manifest suggestive symptoms. However, onconeural antibodies may be detected in individuals without neurologic symptoms. Seropositivity for AQP4-IgG 8 years after onset of optic neuritis suggests that the patient’s blood–brain barrier remained intact, thus restricting entry of these antibodies into the CNS.

This case of NMOSD with AQP4-IgG seropositivity in the context of thyroid cancer expressing high-level AQP4 expands the spectrum of paraneoplastic autoimmunity targeting this antigen.

From Vejle Hospital (K.S., N.A.); Institute of Molecular Medicine (K.S., M.T.M., N.A.), University of Southern Denmark; Odense University Hospital (S.R.L., M.T., K.B., T.J.S., C.G., J.G., S.T.L.), Denmark; Clinical and Experimental Multiple Sclerosis Research Center and NeuroCare Clinical Research Center (F.P.), Charité-Universitätsmedizin Berlin; Experimental and Clinical Research Center (F.P.), Max Delbrueck Center for Molecular Medicine and Charité-Universitätsmedizin Berlin, Germany; and University of Michigan Medical School (T.J.S.), Ann Arbor.

Author contributions: K. Soelberg: study concept and design, acquisition of data, interpretation of results, and writing of manuscript. S.R. Larsen: acquisition of data, revising manuscript, and approving final version. MT. Moerch: acquisition of data, revising manuscript, and approving final version. C. Godballe: interpretation of results.
revising manuscript, and approving final version. M. Thomassen: acquisition of data, revising manuscript, and approving final version. K. Brusgaard: acquisition of data, revising manuscript, and approving final version. F. Paul: interpretation of results, revising manuscript, and approving final version. J. Grauslund: interpretation of results, revising manuscript, and approving final version. S.T. Lillevang: acquisition of data, determination of aquaporin-4 antibodies and other autoantibodies, revising manuscript, and approving final version. N. Asgari: study concept and design, acquisition of data, interpretation of results, revising manuscript, and approving final version, study supervisor.

Acknowledgment: The authors thank The Lundbeck Foundation, The Region of Southern Denmark, and The University of Southern Denmark for support; and the Owens group for discussion. F.P. is supported by Bundesministerium für Bildung und Forschung (Competence Network Multiple Sclerosis).

Study funding: Supported by the Region of Southern Denmark and The University of Southern Denmark.

Disclosure: K. Soelberg received research support from The Region of Southern Denmark and the University of Southern Denmark. S.R. Larsen reports no disclosures. M.T. Moerch received research support from Lundbeck Foundation. C. Godballe serves on the editorial board for European Archives of Otolaryngology and Acta Oncologica. M. Thomassen reports no disclosures. K. Brusgaard served as an editor for PlosOne and Lipidology. F. Paul received speaker honoraria and travel grants from Bayer, Novartis, Biogen Idec, Teva, Sanofi-Aventis/Genzyme, Merck Serono, Alexion, Chugai, MedImmune, and Shire; was on the study steering committee for Novartis and MedImmune; is an Associate Editor for PlosOne and Neurology®; Neuroimmunology & Neuroinflammation; has consulted for Sanofi-Aventis, Biogen Idec, MedImmune, Shire, and Alexion; received research support from Bayer, Novartis, Biogen Idec, Teva, Sanofi-Aventis/Genzyme, Alexion, Merck Serono, German Research Council, Werth Stiftung of the City of Cologne, German Ministry of Education and Research (BMBF Competence Network Multiple Sclerosis), Arthur Arnaust Stiftung Berlin, Guthy Jackson Charitable Foundation, and the US National Multiple Sclerosis Society. T.J. Smith received research support from NIH, Bell Charitable Foundation, RPB Foundation, and Guthy-Jackson Foundation. J. Grauslund serves as editor for ACTA Ophthalmologica. S.T. Lillevang reports no disclosures. N. Asgari received research support from The Vejle Hospital Research Fund of the Region of Southern Denmark, Lundbeck Research Foundation, The University of Southern Denmark. Go to Neurology.org/jn for full disclosure forms. The Article Processing Charge was paid by the authors. This is an open access article distributed under the terms of the Creative Commons Attribution-NonCommercial-NoDerivatives License 4.0 (CC BY-NC-ND), which permits downloading and sharing the work provided it is properly cited. The work cannot be changed in any way or used commercially.

Received April 2, 2016. Accepted in final form May 6, 2016.

Correspondence to Dr. Asgari: nasgari@health.sdu.dk

Aquaporin-4 IgG autoimmune syndrome and immunoreactivity associated with thyroid cancer
Kerstin Soelberg, Stine R. Larsen, Marlene T. Moerch, et al.
Neurol Neuroimmunol Neuroinflamm 2016;3;
DOI 10.1212/NXI.0000000000000252

This information is current as of June 16, 2016

Updated Information & Services
including high resolution figures, can be found at:
http://nn.neurology.org/content/3/4/e252.full.html

References
This article cites 7 articles, 0 of which you can access for free at:
http://nn.neurology.org/content/3/4/e252.full.html##ref-list-1

Subspecialty Collections
This article, along with others on similar topics, appears in the following collection(s):
Autoimmune diseases
http://nn.neurology.org/cgi/collection/autoimmune_diseases
Devic's syndrome
http://nn.neurology.org/cgi/collection/devicssyndrome
Optic neuritis; see Neuro-ophthalmology/Optic Nerve
http://nn.neurology.org/cgi/collection/optic_neuritis
Paraneoplastic syndrome
http://nn.neurology.org/cgi/collection/paraneoplastic_syndrome

Permissions & Licensing
Information about reproducing this article in parts (figures, tables) or in its entirety can be found online at:
http://nn.neurology.org/misc/about.xhtml#permissions

Reprints
Information about ordering reprints can be found online:
http://nn.neurology.org/misc/addir.xhtml#reprintsus

Neurol Neuroimmunol Neuroinflamm is an official journal of the American Academy of Neurology. Published since April 2014, it is an open-access, online-only, continuous publication journal. Copyright © 2016 American Academy of Neurology. All rights reserved. Online ISSN: 2332-7812.