Screening for onconeural antibodies in neuromyelitis optica spectrum disorders

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Abstract

Background: Some so-called “non-classical” paraneoplastic neurological syndromes (PNS), namely optic neuritis and myelitis, clinically overlap with neuromyelitis optica spectrum disorders (NMOSD), and conversely, in cancer-associated NMOSD, a paraneoplastic etiology has been suggested in rare cases. Therefore, we retrospectively investigated the prevalence of onconeural antibodies, which are highly predictive for a paraneoplastic etiology, and the prevalence of malignancies in NMOSD patients.

Methods: We retrospectively screened 23 consecutive patients from our clinic with NMOSD (13 were anti-aquaporin-4 [AQP4] antibody positive, 10 were AQP4 negative) for onconeural antibodies using an immunoblot.

Results: All patients were negative for a broad spectrum of antibodies targeting intracellular onconeural antigens (Hu, Yo, Ri, CV2/CRMP5, Ma1, Ma2, Zic4, SOX1, Tr, and amphiphysin). Notably, only two patients had a malignancy. However, neoplastic entities (astrocytic brain tumor and acute myeloid leukemia) were not typical for PNS.

Conclusions: Our data suggest that there is no need to routinely screen anti-AQP4 antibody positive NMOSD patients with a typical presentation for onconeural antibodies. Furthermore, absence of these antibodies in NMOSD, which is typically non-paraneoplastic, confirms their high specificity for PNS.

Keywords: Aquaporin-4, Neuromyelitis optica spectrum disorders, NMOSD, Onconeural antibodies, Paraneoplastic

Background

Neuromyelitis optica (NMO) is a rare, immune-mediated, demyelinating disorder of the central nervous system (CNS), typically presenting with relapsing optic neuritis (ON) and/or ≥ three vertebral segment longitudinally extensive transverse myelitis (LETM) [1, 2]. Pathogenetic antibodies targeting the water channel protein aquaporin-4 (AQP4) are found in the majority of patients with NMO [3]. Since their discovery, the spectrum of clinical manifestations within the CNS associated with AQP4 antibodies has expanded [4]. Therefore, diagnostic criteria have recently been revised, introducing the term “neuromyelitis optica spectrum disorders (NMOSD)” [5]. According to these revised criteria, an NMOSD diagnosis can also be established in absence of anti-AQP4 antibodies. For simplicity, in the following, the term “NMOSD” is consistently used for both NMO and NMOSD.

Paraneoplastic neurological syndromes (PNS) are remote effects of cancer and often are associated with high concentrations of so-called well-characterized onconeural antibodies (anti-Hu, Yo, Ri, CV2/CRMP5, Ma1, Ma2, and amphiphysin) that help to establish the diagnosis [6]. Notably, some “non-classical” PNS (ON, myelitis) have a clinical presentation similar to NMOSD [6–10]. Conversely, previous studies of cancer-associated NMOSD, comprising mainly case reports, postulated a paraneoplastic etiology [11–17], particularly if the tumor expresses AQP4 [18–22]. However, onconeural antibodies were not systematically investigated in NMOSD.

Regarding a previously suggested paraneoplastic etiology in rare cases, we retrospectively investigated the prevalence of onconeural antibodies and malignancies in NMOSD patients.

Methods

Consecutive patients were identified by an electronic database search. Based on clinical records, NMOSD diagnosis was verified according to recently revised
criteria [5]. This approach identified 35 patients with NMOSD who were treated in our clinic (Department of Neurology and Neurophysiology, Medical Center—University of Freiburg, Germany) between 2003 and 2015. Stored serum samples kept at –80 °C from 25 therapy naïve patients were available for analysis. Of these patients, two declined analysis. Finally, 23 patients entered the study. Demographic and clinical data, including anti-AQP4 antibody status, were obtained from patients’ records.

Screening for antibodies targeting intracellular onconeural antigens (Hu, Yo, Ri, CV2/CRMP5, Ma1, Ma2, Zic4, SOX1, Tr, and amphiphysin) was performed on serum samples using a commercial immunoblot with highly purified recombinant antigens according to the manufacturer’s instructions (kindly provided by ravo Diagnostika, Freiburg, Germany).

Dichotomized variables are presented using numbers and percentages; continuous variables are presented using means or medians, range, and standard deviation (SD). The local ethics committee approved the study, and all patients gave written informed consent to the study protocol.

### Results

Table 1 summarizes clinical data of 23 patients fulfilling revised criteria for NMOSD diagnosis and entering the study. Mean age was 44 years (range 19–75, SD 17.2) at disease manifestation, and 49 years (range 20–75, SD 15.8) at diagnosis. Eighteen (78.3%) were female, and 13 (56.5%) were anti-AQP4 antibody positive. Two patients (Table 1: patients #5 and #15) had a malignoma: one had an anaplastic astrocytoma that occurred 7 years after NMOSD manifestation and that progressed to secondary glioblastoma; the other had acute myeloid leukemia (AML) that was treated with stem cell transplantation 4 years before the NMOSD manifestation. Follow-up information was available in all patients with a median duration of 5.0 years (range 0.5–10.0 years, SD 2.7). Remarkably, none had antibodies targeting intracellular onconeural antigens (Hu, Yo, Ri, CV2/CRMP5, Ma1, Ma2, Zic4, SOX1, Tr, and amphiphysin).

### Discussion

Inspired by previous reports suggesting a paraneoplastic etiology in rare cases of cancer-associated NMOSD,
[11–22], this is the first study systematically investigating the seroprevalence of onconeural antibodies (anti-Hu, Yo, Ri, CV2/CRMP5, Ma1, Ma2, Zic4, SOX1, Tr, and amphiphysin) in NMOSD patients.

The principal finding was that all 23 patients’ samples were antibody-negative. However, we acknowledge that the absence of onconeural antibodies does not exclude PNS [6]. In addition, only two patients in our study had a malignancy; yet neoplastic entities (astrocytic brain tumor and AML) are not typically associated with PNS [6]. By contrast, previous reports on putative paraneoplastic NMOSD described associated malignancies that typically occur in PNS patients, predominantly lung and breast cancer [11–22]. Unfortunately, these reports did not systematically investigate onconeural antibodies for comparison with our data. In this regard, there is currently only one case report describing anti-Hu antibodies in a patient with anti-AQP4 positive NMOSD and recurrent thymoma [23].

Limitations of our study were the retrospective design and therefore patients were not systematically screened for occult malignomas. Furthermore, the case number was limited, since serum was available for only 25 of 35 patients (71.4%) previously identified by an electronic database search for those with an NMOSD diagnosis.

Conclusions
According to our data, the routine screening for onconeural antibodies in NMOSD patients is not mandatory. However, clinicians should pay particular attention in anti-AQP4 negative patients, in patients with a known malignancy or cancer risk factors (e.g. smoking), and/or if clinical presentation is atypical, since paraneoplastic myelitis and/or ON in association with anti-CV2/CRMP5, –Hu or –amphiphysin antibodies might clinically mimic NMOSD [7–10]. Finally, the absence of onconeural antibodies in a typically non-paraneoplastic disorder corresponds to their high specificity for PNS [6]. Finally, larger retrospective trials are necessary to verify these results and to determine the proportion of anti-AQP4 negative NMOSD patients with onconeural antibodies.

Abbreviations
AML: Acute myeloid leukemia; AQP4: Aquaporin-4; CNS: Central nervous system; LETM: Longitudinally extensive transverse myelitis; NMOSD: Neuromyelitis optica spectrum disorder; ON: Optic neuritis; PNS: Paraneoplastic neurological syndromes; SD: Standard deviation

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Availability of data and material
All data generated or analyzed during this study are included in this published article.

Authors’ contributions
BB conceived the study, drafted the manuscript, performed antibody testing, and collected patients’ data. TH collected patients’ data. SR and OS helped to draft the manuscript. All authors read and approved the final manuscript.

Competing interests
BB received travel grants from Bayer Vital GmbH, Ipsen Pharma GmbH, and Genzyme. TH received travel grants from Bayer Vital GmbH and Novartis. OS and SR report receiving consulting and lecture fees, and grant and research support from Baxter, Bayer Vital GmbH, Biogen Idec, Genzyme, Merck Serono, Novartis, Sanofi-Aventis, and Teva. Furthermore, SR is a founding executive board member of ravo Diagnostika GmbH, which sells in-vitro diagnostic medical devices for the detection of infectious diseases and paraneoplastic autoantibodies. None of the authors have any financial or personal relationships with individuals or organizations that could inappropriately influence this publication.

Consent for publication
All patients gave written informed consent to the study protocol and to publication of their data.

Ethics approval and consent to participate
The local ethics committee of the Albert-Ludwigs-University (Freiburg, Germany) approved the study (EK-Freiburg 47/16). All patients gave written informed consent to participate in the study.

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