Published in final edited form as:

Int J Neurosci. 2014 July ; 124(7): 509–511. doi:10.3109/00207454.2013.854208.

Is Neuromyelitis Optica with Advanced Age of Onset a Paraneoplastic Disorder?

Daniel Ontaneda, MD and Robert J Fox, MD

Mellen Center for Multiple Sclerosis Cleveland Clinic, Cleveland, OH, USA

Abstract

Background—Neuromyelitis optica (NMO) antibodies are commonly found in patients with NMO, a relapsing CNS inflammatory disorder. Recent evidence suggests that the NMO antibody may be a paraneoplastic marker. We evaluated this possibility using a health systemwide electronic medical record (EMR), allowing assessment of neoplasm both before and after the assessment of NMO seropositivity.

Design/Methods—An automated search of the Cleveland Clinic EMR was performed to identify patients with NMO serology testing (since 2006). Demographic, clinical, and imaging data were collected, including malignancy history.

Results—Forty-one patients NMO seropositive subjects were found. Average age at first clinical symptom was 38.7 years (SD 15.1), and 33 (80.5%) patients met formal criteria for NMO. Six malignancies were identified in 5 NMO seropositive patients (12.2%; age 48.7 yrs [SD 12.4] at presentation of NMO). Cancers included breast carcinoma (3 cases), lymphoma, cervical carcinoma, and leiomyosarcoma. The timing of malignancy diagnosis varied from 15 years prior to 14 years after the onset of neurologic symptoms. Among seropositive patients over age 50 years at the time of this review, malignancy was seen in 5/25 patients (20%). All 5 subjects fulfilled NMO clinical criteria.

Conclusions—A high prevalence of malignancy was found in NMO seropositive patients, although the sample size was small. These observations support the possibility of NMO as a paraneoplastic marker. If further studies confirm this relationship, clinicians may consider malignancy screening in individuals seropositive for NMO, particularly those over the age of 48.

Search terms

Neuromyelitis optica; paraneoplastic; cancer; myelitis; optic neuritis

Corresponding author: Daniel Ontaneda MD, Mellen Center for Multiple Sclerosis Treatment and Research, Cleveland Clinic Foundation, 9500 Euclid Avenue, U-10, Cleveland, OH, USA foxr@ccf.org.

Author Qualification:

Dr. Ontaneda was responsible for study design, data collection, analysis, manuscript drafting and revising.

Dr. Fox was responsible for study design, data analysis, manuscript revising.

Author disclosures

Dr Ontaneda is supported by a National Institutes of Health (Clinical and Translational Science Collaborative of Cleveland, (KL2TR000440) KL2 Award and a National Multiple Sclerosis Clinical Fellowship Award FP 1769-A-1. Dr. Ontaneda has received consulting or speaking fees from Acorda Therapeutics, Biogen Idec, and Novartis.

Dr. Fox has received grants from the National Multiple Sclerosis society and National Institutes of Health, as well as consulting fees from Avanir, Allosyne, Biogen Idec, Novartis, Questcor, and Teva Neuroscience, and research support from Novartis.

Introduction

Neuromyelitis optica (NMO, or Devic's disease) is a relapsing demyelinating disease of the central nervous system which preferentially affects the spinal cord and optic nerves.¹ The neuromyelitis optica IgG antibody (NMO-IgG) is directed at the aquaporin 4 water channel and is a sensitive and specific marker for NMO. NMO-IgG now forms part of the diagnostic criteria of NMO.²

There have been several case reports of NMO-IgG coincident with cancer, suggesting NMO-IgG possibly being a paraneoplastic marker.^{3–5} This possible association was investigated by Pittock et al⁶ who found that 5% of patients with NMO spectrum disorders and positive NMO-IgG had a history of neoplasm. Additionally, 27% of patients with positive NMO IgG found on routine paraneoplastic serology screening had a history of malignancy, although the laboratory referral base for paraneoplastic serologic testing likely biased the group for increased malignancy.

We sought to describe the incidence of malignancy in patients with positive NMO IgG at our institution and compare that to the incidence of malignancy in a previously published multiple sclerosis (MS) cohort.

Methods

After obtaining institutional review board approval, all patients undergoing NMO IgG antibody testing were identified from the Cleveland Clinic electronic medical record database. Chart reviews were then conducted to obtain demographic data, neurological history, personal history of malignancy, and imaging, CSF, and laboratory studies. A telephone interview was conducted with all seropositive patients to confirm data from the chart review.

Results

A total of 41 patients with positive NMO IgG were identified, and all consented to the study. Mean age at symptom onset for NMO IgG seropositive patients was 38.7 years (SD 15.2), and 38 (92.6%) were female. Average follow-up after symptom onset was 10.6 years (SD 8.2). Among NMO IgG seropositive patients, 33 (80.5%) carried a clinical diagnosis of NMO based upon Wingerchuk criteria.¹ Six malignancies were found in five (12.2%) NMO IgG seropositive patients and 15.2% of NMO IgG seropositive patients with a clinical diagnosis of NMO. Malignancies included breast carcinoma (3 cases), small lymphocytic lymphoma, cervical carcinoma, and leiomyosarcoma (in a patient who also had breast carcinoma). Neurological symptoms preceded the diagnosis of malignancy in 2 subjects, and followed the diagnosis of malignancy in 3 subjects (Table 1). No specific testing looking for malignancy was conducted in the 2 subjects with neurological symptoms preceding diagnosis at the time of diagnosis; rather malignancy was found unrelated to neurological symptoms. All five malignancy associated NMO seropositive cases (MANS) were female and met diagnostic criteria for NMO. Age of onset of NMO symptoms for MANS cases was 48.8 years (SD 12.4), and 36.7 (SD 15.0) for non-MANS cases ($p = 0.046$, one-tailed sided

Student's *t*-test). NMO symptom onset occurred after age 48 in four of the five (80%) MANS patients, but only in 8 of 36 (22%) non-MANS patients.

MRI of the brain and cervical spine was recorded in all NMO IgG seropositive patients, and thoracic spine in 37 patients. Longitudinally extensive spinal cord lesions were observed in all MANS patients and in 78% of Non-MANS patients. Brain MRI abnormalities were noted in all MANS patients, although abnormalities were non-specific (scattered deep non enhancing white-matter T2 hyper intensities) and not typical of those seen in NMO. Other autoantibodies, among MANS patients included positive anti-nuclear antibody titers in 3 of the 5 MANS subjects.

Discussion

The 15.2% malignancy rate we observed in our cohort of NMO patients with positive NMO IgG is three times higher than the 5% previously reported in NMO patients.⁶ A population survey of 8983 MS patients from the North American Research Committee on Multiple Sclerosis (NARCOMS) registry found a cancer rate of 2.9%.⁷ The mean age in the NARCOMS study was 47.4 years (SD 10.0), which was similar to the 48.7 years in our study.

The onset of neurological symptoms occurred at a later age in the MANS patients when compared to the non-MANS group, while the other clinical and radiological features of NMO were similar between MANS and non-MANS patients. Four of the five MANS patients had symptom onset after the age of 48. The later age of onset in MANS is similar to the cases described previously.⁶

Although our sample size is small, our observations suggest that NMO may occur in a paraneoplastic context, particularly in patients with more advanced age of onset (i.e. after age 48). These preliminary findings need to be replicated in a larger, more broad-based population sample. If confirmed, the increased prevalence of malignancy in NMO patients may represent a clinically relevant finding and suggests that malignancy screening be considered in NMO patients, particularly those presenting beyond the age of 48 years.

Acknowledgments

The study was supported by a research grant from the National Multiple Sclerosis Society (USA) FP 1769-A-1 to D.O.

References

1. Wingerchuk DM, Lennon VA, Lucchinetti CF, Pittock SJ, Weinshenker BG. The spectrum of neuromyelitis optica. *Lancet Neurol*. 2007 Sep; 6(9):805–815. [PubMed: 17706564]
2. Wingerchuk DM, Lennon VA, Pittock SJ, Lucchinetti CF, Weinshenker BG. Revised diagnostic criteria for neuromyelitis optica. *Neurology*. 2006 May 23; 66(10):1485–1489. [PubMed: 16717206]
3. De Santis G, Caniatti L, De Vito A, De Gennaro R, Granieri E, Tola MR. A possible paraneoplastic neuromyelitis optica associated with lung cancer. *Neurol Sci*. 2009 Oct; 30(5):397–400. [PubMed: 19565183]

4. Mueller S, Dubal DB, Josephson SA. A case of paraneoplastic myelopathy associated with the neuromyelitis optica antibody. *Nat Clin Pract Neurol*. 2008 May; 4(5):284–288. [PubMed: 18317500]
5. Antoine JC, Camdessanche JP, Absi L, Lassabliere F, Feasson L. Devic disease and thymoma with anti-central nervous system and antithymus antibodies. *Neurology*. 2004 Mar 23; 62(6):978–980. [PubMed: 15037705]
6. Pittock SJ, Lennon VA. Aquaporin-4 autoantibodies in a paraneoplastic context. *Arch Neurol*. 2008 May; 65(5):629–32. [PubMed: 18474738]
7. Marrie R, Horwitz R, Cutter G, Tyry T, Campagnolo D, Vollmer T. Comorbidity, socioeconomic status and multiple sclerosis. *Mult Scler*. 2008 Sep; 14(8):1091–8. [PubMed: 18728060]

Table 1

Clinical and Laboratory Characteristics

	Malignancy Associated NMO Ab (MANS)	Non Malignancy Associated NMO Ab (Non-MANS)
Total (n)	5	36
Age at onset (mean, SD)	48.8, 12.4	36.6, 15
Female gender (n, %)	5, 100	33, 92
Follow-up from onset (mean years, SD)	11.8, 12.3	10.5, 7.7
Diagnosis of NMO (n, %)	5, 100	28, 78
Myelopathy (n, %)	5, 100	35, 97
Bilateral optic neuritis (n, %)	2, 40	16, 44
Unilateral optic neuritis (n, %)	3, 60	13, 36
CSF IgG index (n, %)	3, 100	6, 46
CSF IgG synthesis rate (n, %)	3, 100	6, 46
Oligoclonal bands (n, %)	1, 33	3, 27

Paraneoplastic NMO cases				
Age at Onset	Gender	Ethnicity	Malignancy	Time of diagnosis of NMO to time of Malignancy (years)
51	F	African American	Breast carcinoma, leiomyosarcoma	6
64	F	Caucasian	Small lymphocytic lymphoma	-15
30	F	African American	Cervical carcinoma	-2
50	F	Caucasian	Breast carcinoma	-1
48	F	African American	Breast carcinoma	3