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NMO-IgG (Aquaporin-4) autoantibodies in immune-mediated optic neuritis

A. Petzold [a,b], S. Pittock [e,f] V. Lennon [e,f,g] C. Maggiore [b]
B.G. Weinshenker [e] G.T. Plant [b,c,d]

aDepartment of Neuroinflammation, Institute of Neurology, University College London, Queen Square, London WC1N 3BG, UK
bNational Hospital for Neurology and Neurosurgery, Queen Square, London, WC1N 3BG, UK
cMoorfields Eye Hospital, Department of Neuro–ophthalmology, City Road, EC1 2PD, UK
dMedical Eye Unit, St. Thomas' Hospital, Lambeth Palace Road London, SE1 7EH, UK
eDepartment of Neurology, Mayo Clinic College of Medicine, Rochester, MN 55905, USA
f Department of Laboratory Medicine and Pathology, Mayo Clinic College of Medicine, Rochester, MN 55905, USA
g Department of Immunology, Mayo Clinic College of Medicine, Rochester, MN 55905, USA

Abstract

The clinical course of immune–mediated optic neuritis (ON) will depend upon the specific underlying inflammatory disease. These disorders have traditionally been classified according to clinical and magnetic resonance imaging (MRI) findings. Aquaporin-4 (AQP4) autoantibodies (NMO-IgG) may have diagnostic and prognostic value in patients who present with isolated ON. In this prospective study we evaluated NMO-IgG in 114 patients with optic neuritis in the following contexts: neuromyelitis optica (NMO), multiple sclerosis (MSON), chronic relapsing inflammatory optic neuropathy (CRION), relapsing isolated optic neuritis (RION), and single isolated ON (SION). The proportion seropositive was 56% for NMO (n=9), 0% for MSON (n=28) and 5% for the remaining diagnostic categories (CRION (n=19), RION (n=17) and SION (n=41)). Testing for NMO-IgG in patients with recurrent or severe ON who lack convincing evidence of MS may identify patients who would benefit from immunosuppression rather than MS-directed immunomodulatory therapies.

Key words: optic neuritis, CRION, NMO, aquaporin-4 antibody

Introduction

In 2004 Lennon *et al.* reported their discovery of an IgG antibody which is highly specific for patients suffering from neuromyelitis optica (NMO) [1]. The autoantibody marker (NMO-IgG) assists in the distinction between neuromyelitis optica (NMO) and multiple sclerosis (MS). NMO-IgG reacts with the water channel protein aquaporin–4 (AQP4) [2] that is concentrated in the astrocytic foot processes that extend to the abluminal surface of blood vessels. Staining by NMO-IgG in a diffuse mesh–like and vasculocentric pattern is intense in the optic nerve [3].

In the initial report from the Mayo Clinic, 2 of 8 patients (25%) with relapsing isolated optic neuritis (RION) were seropositive [1]. Similarly a more recent series from Mayo Clinic reported that 5 of 25 patients (20%) with non-MS recurrent optic neuritis were seropositive. Seropositivity for NMO-IgG predicted a poor visual outcome and myelitis subsequently occurred in 6 of 12 seropositive patients evaluated either at the Mayo Clinic or at other institutions for recurrent optic neuritis which was isolated at the time of serological testing [4]. Four of 21 (19%) of French patients with ON all of whom had a normal brain MRI and suffered from severe irreversible visual loss were NMO-IgG seropositive [5]: A collaborative Spanish–Italian study found 1/7 (14%) patients with RION to be seropositive for NMO-IgG [6]; that patient had severe ON and brain MRI was normal, consistent with features typical of NMO-associated optic neuropathy [6]. The relationship of such NMO-IgG seropositive cases to those described clinically by Kidd *et al.* as chronic relapsing inflammatory optic neuropathy (CRION) [7, 8] has been uncertain. Management of patients with CRION differs fundamentally from that of multiple sclerosis-associated optic neuritis (MSON) [8]. The key feature that differentiates CRION from MSON is the prominent tendency to relapse on withdrawal of steroids. Many of the original cases from the London cohort, some of whom have been followed for over 25 years, have required long–term immunosuppression.

We investigated whether serum NMO-IgG may be detectable in CRION patients. Our hypothesis was that CRION may be part of the expanding spectrum of NMO.

Patients and Methods

Patients

One hundred and fourteen patients presenting with unilateral or bilateral isolated ON were recruited prospectively in three London hospitals (Moorfields Eye Hospital, The National Hospital for Neurology and Neurosurgery and the Medical Eye Unit at St. Thomas' Hospital) between November 1995 and September 2007. Inclusion criteria were: progressive loss of vision over a few days, decreased visual acuity (Snellen chart), decreased colour vision (Ishihara colour plates) and a relative afferent pupillary defect (unless bilateral and symmetrical) [9]. Exclusion criteria were: any previous neurological episode and any macular or retinal pathology. The study was approved by the local and national ethics committees.

Patients were classified according to clinical criteria and response to treatment into one of five inflammatory optic neuropathies:

1. ON as seen typically in MS (MSON); patients fulfilling the clinical and imaging criteria for MS [10].
2. ON in Neuromyelitis optica (NMO); patients fulfilling the revised clinical and imaging criteria for NMO [11].
3. Chronic Relapsing Inflammatory Optic Neuritis (CRION); patients who require immunosuppression to prevent a relapse of ON and who have neither imaging nor clinical evidence of myelitis after a follow up period of at least one year [7].
4. Recurrent isolated ON (RION); spontaneous and isolated recurrence of unilateral ON (one or both nerves may be affected in recurrent attacks) in patients who do not have MS and are not immunosuppressed.
5. A solitary episode of isolated optic neuritis (SION); patients with unilateral or bilateral ON but no evidence for MS, who have not required long term immunosuppression and have not experienced a recurrence of optic neuritis nor any other neurological episode after at least one year of follow up. [9].

Blood samples

Serum samples were tested for NMO-IgG at the Mayo Clinic laboratories by indirect immunofluorescence on a substrate of mouse cerebellum and midbrain as described previously [1]. Blood samples were coded and aliquots send to the Mayo Clinic for analysis were double coded in order mask all participants. Data were exchanged between the centres by a telephone conference during which the double code was broken.

Imaging

Conventional brain and optic nerve MR imaging was performed using 1.5 Tesla systems at both, the National Hospital for Neurology and Neurosurgery and at St Thomas' Hosptial and consisted of axial and coronal T1 and T2 weighted spin echo and FLAIR MR imaging [9]. Imaging of the spinal cord was only carried out if patients developed symptoms of myelitis.

Data analysis

Data analysis was performed using SAS (V9.2). Because of non-Gaussian data distribution the median and interquartile range are shown.

Results

The patient characteristics are shown in Table 1. Four of the patients recruited were from the original CRION cohort [7] who continue to be followed up at the National Hospital for Neurology and Neurosurgery.

Serum NMO-IgG was detected in 56% of NMO patients and none of the MSON patients (Table 1). In all of the remaining diagnostic categories (CRION, RION and SION) the seropositive rate was 5%.

Discussion

Consistent with previous reports the proportion of NMO-IgG seropositive NMO patients was in the 50–60% range [1, 5, 6, 12, 13]. Equally we can confirm the high specificity of this test to distinguish patients with a full clinical diagnosis of NMO from those with a full clinical diagnosis of MS as none of the MS patients was seropositive for NMO-IgG.

The low rate of seropositivity in CRION, RION and SION compared to NMO suggests that although patients with non-MS ON may have an early or limited form of NMO, it probably accounts for a small minority of cases of these clinically-defined types of optic neuritis. A second alternative is that the titres of NMO-IgG are uniformly lower in this population, and thus, the antibody is less likely to be detected. None of the four CRION cases from the original cohort described by Kidd *et al.* were seropositive for NMO-IgG.

Prospective follow-up of our cohort is needed to determine whether or not seropositivity predicts development of NMO in these patients. All patients in the NMO and CRION groups in this series were immunosuppressed at the time of testing. Therefore, it is unlikely that immunosuppression was responsible for the low rate of seropositivity in CRION considering the high rate in the NMO subgroup, although it is impossible to say whether this did not contribute in certain individuals. Disease activity and treatment-related fluctuation in titer has been reported in 8 Caucasian [14] and 3 Asian patients [15] with NMO who were repeatedly tested. Therefore repeat testing of seronegative CRION and RION patients during relapse may be required.

Thus, NMO-IgG testing may help identify a small subgroup of patients with isolated or recurrent non-MS optic neuritis, constituting between 5-25% of patients, who may benefit from more aggressive treatment of the acute episode and from longer term immunosuppression rather than from immunomodulatory therapies currently prescribed to patients with MSON. Further studies will clarify the exact proportion and other clinical and demographic factors that distinguish these groups. Meanwhile we recommend testing for NMO-IgG in all patients with recurrent or severe

optic neuritis particularly when there is no evidence of MS. Furthermore a negative test does not preclude the subsequent development of NMO nor of a relapsing optic neuritis requiring immunosuppression but a positive test does make a diagnosis of MS highly unlikely.

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Conflict of interest and source of funding

A Petzold, C Maggiore, S. J. Pittock,and GT Plant have no conflict of interest and nothing to disclose. This study was not funded.

V.A. Lennon and B Weinshenker have intellectual property associated with the discovery of NMO-IgG, which has been licensed to a commercial entity. The NMO-IgG test is offered on a service basis by Mayo Collaborative Service Inc., an agency of Mayo Foundation.

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Table 1: *Characteristics of patients expressed as medians (interquartile range), numbers (%), ANA = antinuclear antibodies, AZT = azathioprine, CSF = cerebrospinal fluid, PE = plasma exchange, OCB = oligoclonal bands, RF = rheumatoid factor, VA = visual acuity.*

Feature	MSON	SION	RION	CRION	NMO
N	28	41	17	19	9
Median age at onset (years)	33	42	37	45	29
range	23–50	15-71	20–69	29–69	25–69
Female : Male	17:11	26:15	13:4	14:5	6:3
Autoimmune co-morbidity	0/28 (0%)	4/41 (10%)	1/17 (6%)	1/19 (5%)	1/9 (11%)
Serology (where tested)					
ANA	0/6 (0%)	2/16 (13%)	0/4 (0%)	0/10 (0%)	1/5 (20%)
RF	0/1 (0%)	0/10 (0%)	0/4 (0%)	0/8 (0%)	0/4 (0%)
Anti thyroid antibodies	Not tested	0/3 (0%)	0/4 (0%)	0/4 (0%)	0/1 (0%)
Treatment (Rx)					
Steroids	4/28 (14%)	16/41 (39%)	16/17 (94%)	19/19 (100%)	7/7 (77%)
AZT	1/28 (4%)	5/41 (12%)	4/17 (24%)	10/19 (53%)	3/7 (43%)
PE	0/28 (0%)	1/41 (2%)	0/17 (0%)	3/19 (16%)	1/7 (14%)
Other	0/28 (0%)	5/41 (12%)	1/17 (6%)	5/19 (26%)	3/7 (43%)
Treatment at sampling	1/23 (4%)	11/25 (44%)	6/8 (75%)	19/19 (100%)	9/9 (100%)
Follow-up period (months)	5 (1-7)	30 (12-47)	83 (63-175)	50 (21-130)	67 (37-159)