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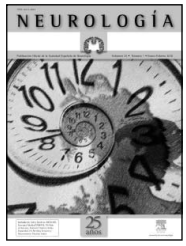

ORIGINAL ARTICLE

Clinical spectrum associated with aquaporin-4 antibodies (NMO-IgG)

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Clinical spectrum associated with aquaporin-4 antibodies (NMO-IgG)

Abstract
Introduction: The description of a highly sensitive and specific biomarker for neuromyelitis optica (NMO-IgG/aquaporin-4 antibody) extended the clinical spectrum of NMO to limited forms such as optic neuritis (ON) and longitudinally extensive myelitis (LEM).
Objective: To asses the sensitivity and specificity of our assay, and to describe the clinical characteristics of the patients who were tested for NMO-IgG.
Methods: NMO-IgG was analysed by immunohistochemistry and confirmed by assay on HEK cells transfected with aquaporin-4. The clinical information was obtained from forms filled in by the referring neurologists.
Results: A total of 580 samples from 518 patients were analysed from November 2005 to September 2008. Clinical information was available from 358 (68%) patients. All 33 (100%) positive cases were followed up. Twenty-eight of the 43 (65%) patients diagnosed with NMO by the revised criteria of 2006 were positive; the sensitivity was 62.5% when applying the same criteria, but discounting the criterion of NMO-IgG status, or 57% when applying the criteria of 1999. NMO-IgG was detected in 3 (13%) of the recurrent LEM and 2 (4%) of the recurrent ON. NMO-IgG was not detected in the remaining patients (96 with a final diagnosis of multiple sclerosis; 80 with myelitis; 28 with non-recurrent ON; and 33 other diagnosis).
Conclusions: No false positive cases were found in this large and non-selected study. NMO-IgG positive cases were mostly associated with NMO, and only in a low percentage with recurrent ON or LEM.

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PALABRAS CLAVE
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Acuaporina 4;
Mielitis transversa;
Neuritis óptica

Espectro clínico asociado a anticuerpos contra aucoporina 4 (IgG-NMO)

Resumen
Introducción: Los anticuerpos IgG-NMO se han demostrado sensibles y específicos para el diagnóstico de neuromielitis óptica (NMO) y han permitido ampliar el espectro clínico a formas limitadas como neuritis óptica (NO) o mielitis longitudinalmente extensas (MLE).
Objetivo: Evaluar la sensibilidad y la especificidad de nuestra técnica y describir las características de los pacientes para los que se solicita dicha determinación.
Métodos: Los anticuerpos IgG-NMO se analizaron mediante inmunohistoquímica y se confirmaron sobre células HEK transfectadas con acuaporina 4. La información clínica se obtuvo mediante un cuestionario rellenado por el neurólogo remitente de la muestra.
Resultados: Desde noviembre de 2005 a septiembre de 2008 se analizaron 580 muestras de 518 pacientes. Se obtuvo información de 358 (68%) pacientes. El seguimiento en los 33 casos positivos fue del 100%. De los 43 pacientes diagnosticados de NMO por los criterios de 2006, 28 (65%) eran positivos; la sensibilidad fue del 62,5% si se aplicaban estos criterios eliminando el resultado de IgG-NMO y del 57% aplicando los criterios de 1999, que tampoco incluyen los IgG-NMO. Se detectaron IgG-NMO en 3 (13%) de las MLE recurrentes y 2 (4%) de las NO recurrentes. No se detectaron IgG-NMO en el resto de los pacientes evaluados (96 finalmente diagnosticados de esclerosis múltiple; 80 mielitis; 28 NO no recurrentes; 33 con otros diagnósticos).
Conclusiones: En este estudio no seleccionado y tan amplio, no se han detectado falsos positivos. Los casos positivos se asocian mayoritariamente con NMO y sólo en un pequeño porcentaje con NO o MLE recurrente.

Introduction

Neuromyelitis optica (NMO) is an inflammatory demyelinating disease, usually severe, which predominantly affects the optic nerve and spinal medulla[1]. The discovery of a specific serological marker[2,3], NMO-IgG or aquaporin-4 antibodies, has enabled: *a*) the expansion of the clinical spectrum to include partial or limited forms of the disease such as recurrent optic neuritis (ON) or longitudinally extensive myelitis (LEM)[1,2,4-6]; *b*) the proposal of new diagnostic criteria that recognise clinical manifestations or through magnetic resonance imaging (MRI) outside the optic nerve or the medulla[7,8], and *c*) the confirmation that it is disease with a different etiopathogenesis from that of multiple sclerosis[9-11].

The prevalence of the disease is poorly understood, although it is considered a rare disease in Caucasian populations, with a rate below 1% of cases of demyelinating diseases[1]. Depending on the technique used in the analysis of NMO-IgG and the diagnostic criteria applied, there have been descriptions of up to 10-46% of patients with NMO being seronegative and that false positives can reach up to 10%[12,13]. The availability of a technique may cause an increase in the number of patients in whom the disease is suspected, which could lead to more cases being diagnosed. However, it could also generate an increase in the number of false positives inherent to the diagnostic technique.

In our laboratory, the determination of NMO-IgG began in November 2005. The aim of this study was to evaluate the sensitivity and specificity at our laboratory and to describe the characteristics of patients for whom this determination was sought.

Patients and methods

We reviewed the database of samples sent to the Neuroimmunology Laboratory of the Barcelona Hospital Clinic for the determination of NMO-IgG between November 2005 and June 2008. Clinical data were collected through a survey sent by the requesting neurologists through an established template or by telephone interview. This survey described, in addition to demographic variables, the items included in the diagnostic criteria for NMO from 1999[14], the number and the type of episodes, concomitant autoimmune diseases, treatments undergone and the score on the Kurtzke expanded disability status scale (EDSS)[15] at the last follow-up and in diagnosis.

The definitive diagnosis of NMO was established by applying the updated 2006 criteria[7]; patients with acute transverse myelitis and medullar MRI with lesion $\geq$ 3 vertebral bodies were classified as LEM; the diagnosis of multiple sclerosis (MS) was established following the McDonald criteria[16]; and that of ON and other diagnoses was based on the final diagnosis of the referring physicians.

NMO-IgG was determined by immunohistochemistry using frozen sections of rat hippocampus and a technique of avidin-biotin-peroxidase (1:500 serum dilution) as was described previously[8,17]. All positive cases were confirmed by immunohistochemistry on HEK cells transfected with