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Clinical utility of anti-MOG antibody testing in a Danish cohort

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ABSTRACT

Background: Anti-myelin oligodendrocyte glycoprotein (MOG) antibody (Ab) can be found in different immune-mediated inflammatory CNS disorders. The full range of clinical manifestations may not have been fully discovered yet.
Methods: In a cross-sectional study 184 adults (age ≥ 16) were tested for anti-MOG antibody (Ab) with a cell-based assay. To define the relevant target population for anti-MOG antibody testing in a neurology clinic, we divided the entire study population based on the presenting symptoms and classified cases followed for multiple sclerosis (MS) according to the clinical features and response to disease-modifying therapy.
Results: We identified eight (4.4%) MOG-Ab positive cases in the whole cohort. All eight cases had first manifestations suggestive of neuromyelitis optica spectrum disorder (NMOSD), but had highly variable disease courses and responses to therapy. This included a patient with chronic relapsing inflammatory optic neuropathy (CRION) responding only to therapy with infliximab. Four (3%) out of 134 cases followed for MS who tested positive for anti-MOG Ab showed atypical features and had poor response to therapy.
Conclusion: A broad range of clinical and radiological features of anti-MOG associated disorder was observed in a single centre. MOG-Ab testing should be considered in patients with an NMOSD phenotype and in MS patients presenting atypical features. The potential use of infliximab therapy for MOG-Ab disease should be further investigated.

1. Introduction

New entities of antibody-mediated CNS disorders have been discovered in the last decade. One of these antibodies targets myelin oligodendrocyte glycoprotein (MOG) located on the outer surface of the myelin sheath (Bradl et al., 2018). Anti-MOG antibody (Ab) has been detected in a broad range of conditions such as seronegative neuromyelitis optica spectrum disorder (NMOSD), optic neuritis (ON), transverse myelitis (TM), acute disseminated encephalomyelitis (ADEM), and encephalopathic syndromes (dos Passos et al., 2018; Jarius et al., 2016b; Jurynczyk et al., 2017; Ramanathan et al., 2018; Waters et al., 2016). MOG-Ab has rarely been found in adult multiple sclerosis (MS) patients and it was mainly restricted to patients with predominantly severe ON, TM and brainstem attacks; and patients showing high disease activity despite treatment with different disease-modifying therapies (DMT) (Spadaro et al., 2016). Due to overlapping features it may still be challenging to reach the correct diagnosis among NMOSD, MS and MOG-Ab-associated diseases, which is important for selecting the appropriate therapy. The following questions can be raised: (I) which patients followed with a diagnosis of MS should be reassessed and tested for MOG-Ab, (II) whether it is applicable to maintain the MS diagnosis in cases where MOG-Abs are detected. Indeed, the McDonald criteria for MS require that there should not be better explanation for the presented symptoms (Polman et al., 2011; Thompson et al., 2018). (III) Whether we have already discovered the full range of MOG-Ab-associated clinical syndromes.

In this study, we studied 184 adult patients who were followed for MS or were newly referred to the MS clinic with a suspected inflammatory CNS disorder for whom a MOG-Ab test was requested. The aim of the study was to evaluate the utility of MOG-Ab test in clinical practice in order to guide physicians to select the relevant patient population for MOG-Ab screening.

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2. Methods

2.1. Study design

This single centre, cross-sectional study recruited adult patients (age ≥ 16) from a highly specialized department of a tertiary hospital, the Danish Multiple Sclerosis Center at Rigshospitalet (Copenhagen, Denmark). Patients reviewed in the MS centre between April 2015 and April 2017 were tested for MOG-Ab. The analysis was carried out in the Autoimmune Neurology Laboratory at John Radcliffe Hospital in Oxford using live transfected cell-based assay (CBA) as described previously (Waters et al., 2015). Anti-aquaporin-4 antibody (AQP4) positivity was confirmed by CBA in the same laboratory in Oxford if screening by enzyme-linked immunosorbent assay (ELISA: EA111/96 kit, DLD Diagnostika GMBH, Hamburg, Germany) at Rigshospitalet was positive.

2.2. Case assessment

First, we divided the study population into two groups: (I) *suggestive of NMOSD* and (II) *suggestive of MS* based on the first clinical manifestation and initial MRI according to 2015 IPND criteria for NMOSD and 2017 revisions of the McDonald criteria for MS (Fig. 1(A)) (Thompson et al., 2018; Wingerchuk et al., 2015). The group *suggestive of NMOSD* was defined as patients presenting with at least one of the NMOSD core clinical symptoms and MRI showing NMOSD-typical brain lesion, longitudinally extensive transverse myelitis (LETM), other large cerebral lesions, normal brain MRI, or findings not meeting dissemination in space (Wingerchuk et al., 2015). The group *suggestive of MS* included patients with a clinically isolated syndrome (CIS) associated with MRI lesions typical of MS (Thompson et al., 2018).

A second assessment focused on the patient population treated for MS at the time of the MOG-Ab test. Here, our cohort was classified in two groups such as (I) *MS/CIS with typical features* and (II) *MS/CIS with atypical features* (Fig. 1(B)). The following characteristics were considered atypical: predominantly ON, TM, brainstem symptoms, seizures, behaviour changes, absence of immunoglobulin G oligoclonal bands (OCB), NMOSD-typical brain lesions, LETM, or other large cerebral lesions besides MS lesions (Thompson et al., 2018; Wingerchuk et al., 2015). Both groups were subdivided based on the response to DMT and no treatment. We considered the therapy response poor when the patient had severe attacks on DMT or disease activity despite therapy with a second-line treatment.

2.3. Protocol approvals

The study was approved by a Regional Ethical Committee (J no. 1-10-72-346-15) and the Danish Data Protection Agency (J no. 1-16-02-658-15). Based on Danish legislation, the Scientific Ethics Committee waived the need for informed patient consent since the study was based solely on patient chart reviews.

3. Results

3.1. Identification of the anti-MOG positive patients

Samples (194) from 184 patients were tested for MOG-Ab. We excluded two patients from further analysis due to incomplete examination (MRI was not performed). The final diagnosis of the 182 was MS ($N = 134$), clinically isolated syndrome ($N = 11$), acute demyelinating encephalomyelitis ($N = 2$), AV fistula ($N = 1$), tumour ($N = 2$), chronic lymphocytic inflammation with pontine perivascular enhancement responsive to steroids ($N = 1$), LETM ($N = 4$), idiopathic transverse myelitis ($N = 7$), necrotizing myelitis ($N = 2$), post-infectious encephalomyelitis ($N = 1$), NMDA-Ab encephalitis ($N = 1$), AQP4-Ab positive NMOSD ($N = 4$), double seronegative NMOSD ($N = 1$),

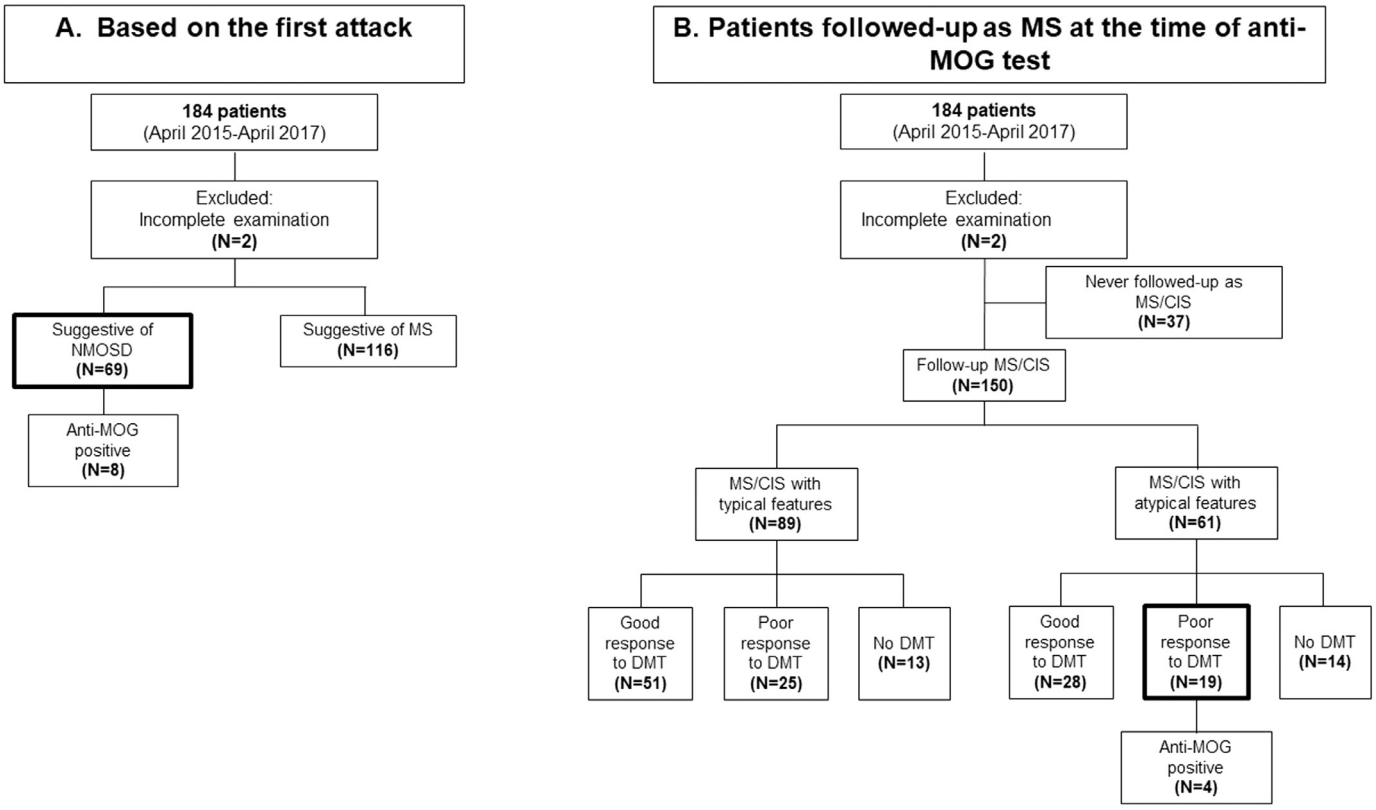

Fig. 1. (A and B). Flow diagram of the study population. MS: multiple sclerosis, CIS: clinically isolated syndrome, NMOSD: neuromyelitis optica spectrum disorder, DMT: disease modifying therapy, Anti-MOG: anti- myelin oligodendrocyte glycoprotein.