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Neuromyelitis optica with clinical and histopathological involvement of the brain

GJD Hengstman, P Wesseling, CWGM Frenken and PJH Jongen

Diagnostic criteria for neuromyelitis optica (NMO) state that there should be no active disease outside the optic nerves and spinal cord. However, several cases have been described with symptomatic brain involvement. We describe an autopsy case of a patient with NMO and symptomatic involvement of the brain. The histopathology of the brain lesions is typical for NMO, with extensive macrophage infiltration, including perivascular accumulation of large numbers of eosinophils. This is the first case that clearly shows that in NMO, the histopathology of the brain lesions is identical to that of the lesions in the optic nerves and spinal cord.

Key words: cerebral; devic; histopathological; neuromyelitis optica

Introduction

Neuromyelitis optica (NMO) is a demyelinating disease with selective involvement of the optic nerves and spinal cord. The disease can be either monophasic or relapsing [1]. Besides the selective involvement of the optic nerves and spinal cord, there are several other features of NMO that distinguish this rare disorder from ‘typical’ multiple sclerosis (MS), including >50 cells/mm³ in the cerebrospinal fluid (CSF), normal initial brain magnetic resonance imaging (MRI), and lesions extending over three or more vertebral segments of the spinal cord MRI [1]. The pathology of active lesions in NMO also differs from that seen in MS [2]. In addition to extensive macrophage infiltration, the inflammatory infiltrates in active NMO lesions contain large numbers of (perivascular) eosinophils [2]. Furthermore, there appears to be a pronounced perivascular deposition of immunoglobulins and complement associated with vascular fibrosis and hyalinization, suggesting a more humoral mediated pathogenesis [2].

Diagnostic criteria for NMO have been published and require, besides the presence of optic neuritis and acute myelitis, the absence of clinical disease outside the optic nerve or spinal cord [1]. However, recently it was shown that a large number of patients with NMO have brain lesions on MRI, usually asymptomatic, but occasionally symptomatic [3]. Whether these lesions have the typical NMO pathological features is unknown. A recently described autopsy case of NMO showed the presence of macrophages phagocytizing myelin debris in the tissue surrounding a large cavitary cerebral lesion [4]. Based on their finding, the authors concluded that this histopathology was similar to that of NMO [4]. However, they did not observe the infiltration of eosinophils that is so typical for NMO, and distinct from MS, in the tissue surrounding the cavity. Here, we present a patient with otherwise typical relapsing NMO that did show, not only cerebral involvement at the clinical level, but also prominent infiltration of eosinophils in and around the lesions throughout the brain.

Case report

A 33-year-old woman with a previous medical history of subclinical hypothyroidism, pancreatitis, and dyspepsia, presented at the outpatient clinic of
a regional general hospital with subacute loss of vision of the left eye accompanied by retro-orbital pain. At that time she was using omeprazol, cisapride, pancreatine, diazepam, and temazepam. MRI of the brain revealed no abnormalities, and she was diagnosed with optic neuritis. Treatment with intravenous methylprednisolone (IVMP) 1000 mg for five consecutive days was initiated, after which a rapid clinical improvement was seen.

Two months later, she developed paraparesis and hypeaesthesia below thoracic level 8. MRI of the spinal cord showed several T2-hyperintense lesions at C2–3, C4–5, Th4, and Th5–6. Examination of the CSF showed pleiocytosis (61 leucocytes/mm³), elevated protein concentration (1.02 mg/L), normal glucose level, and no oligoclonal bands. Again, she was treated with IVMP, resulting in a near-complete clinical recovery.

Within a few weeks, however, the patient developed increased spasticity of the lower extremities, accompanied by slight weakness of the upper extremities and Hermitte’s sign. This was followed within a few days by the occurrence of hemiparalysis on the left side. MRI examination of the brain revealed a large T2-hyperintense lesion involving the basal ganglia on the right side and the adjacent white matter, and several small white matter lesions within the centrum semiovale, corpus callosum, and right cerebral peduncle. Treatment with high-dose IVMP only resulted in partial improvement, and treatment with interferon-beta 1b was initiated.

Over the following 18 months, the patient suffered from several attacks of optic neuritis involving both sides, and had two relapses involving the cervical spinal cord, resulting in severe disability with tetraparesis, severe hypeaesthesia from the cervical level down, and severely impaired vision. Treatment with interferon-beta 1b was eventually stopped because of lack of therapeutic effect. In the meantime, she also had been treated unsuccessfully with intravenous immunoglobulins. The patient died two years after the initial presentation due to respiratory failure.

After her death, an autopsy was performed following consent. Macroscopic examination of the brain and spinal cord revealed multiple white matter lesions, the largest located in the temporal lobe on the right side, corpus callosum, occipital lobe, and the thoracic segment of the spinal cord (Figure 1). Especially in the thoracic spinal cord,
both white and grey matter showed extensive damage (Figure 1E).

Histopathological examination revealed typical NMO abnormalities in the spinal cord, optic nerves and chiasm. The lesions in the brainstem and cerebrum were (also) characterized by extensive myelin loss, a variable but often large number of macrophages, and dispersed, especially perivascular, sometimes extensive accumulation of eosinophils (Figure 2). Interestingly, the latter infiltrate was occasionally found without adjacent demyelinating lesion. In and around the demyelinating lesions, variable reactive astrocytosis was present.

Discussion

Neuromyelitis optica, or Devic’s disease, is regarded as a specific disease within the group of acquired immune-mediated demyelinating diseases of the central nervous system, of which MS is the most important representative. Due to its preferential involvement of the optic nerves and spinal cord, NMO not only differs clinically from ‘typical’ MS, but also the CSF abnormalities, MRI characteristics, and histopathology separate NMO from other forms of acquired demyelinating central nervous system diseases [1,2]. The hallmark of NMO is the selective involvement of the optic nerves and spinal cord, with sparing of the brain. The reason why the brain is spared is unknown, but this remarkable clinical characteristic is included in the diagnostic criteria and is a prerequisite for making the diagnosis NMO [1].

Several reports, though, have indicated that the brain may be involved in the disease process after all [3,5]. In a recent study of 60 patients with NMO, brain lesions were detected on MRI in 60% of the cases [3]. These lesions were occasionally symptomatic and some fulfilled the Barkhof et al. criteria for MS lesions. Histopathology was performed in one of the included patients, but the biopsy specimen, showing an inflammatory demyelinating lesion, was too small for extensive analysis.

Figure 2  Microscopy showing a prominent admixture of eosinophils (indicated by arrows) in the inflammatory infiltrate in corpus callosum (A, B) and base of the pons (C, D). The area in the rectangles in (A) and (C) are shown at higher magnification in (B) and (D), respectively. The infiltration of eosinophils in the corpus callosum occurs in a demyelinating lesion with dispersed accumulation of macrophages (arrowheads); the asterisk in (A) indicates the transition to normal white matter. In the level shown of the pons, the eosinophilic infiltrate is not (yet) accompanied by demyelination. Some neurons in the pontine nuclei show hypereosinophilic change and pycnosis (arrowheads in (D)), consistent with recent hypoxic damage. (A)–(D) Hematoxylin and eosin staining, original magnification ×100 (A, C), and ×400 (B, D).
The recently described autopsy case of a patient with NMO and a symptomatic cerebral lesion also clearly showed that the brain can be involved in this disease [4]. However, on histopathological examination, no active inflammation was found in the brain, therefore, that the process affecting the brain was of the same kind as that affecting the optic nerves and spinal cord was not conclusive. The case that we describe clearly shows that symptomatic inflammatory lesions in the brain can occur in NMO, and that these lesions resemble typical NMO lesions with extensive macrophage infiltration, including accumulation of large numbers of perivascular eosinophils. The disease in this patient fulfills the diagnostic criteria for NMO, with the exception of the absence of active disease outside the optic nerves and spinal cord [1]. The histopathological features further support the diagnosis NMO. The presence of NMO-IgG, a recently discovered autoantibody specific for NMO, was not determined because this test was not available at that time.

The question remains why the disease preferentially involves the optic nerves and spinal cord. The most likely cause involves antigenic characteristics driving the immune response, which apparently are unique to these structures of the central nervous system. As it has been suggested that the underlying pathogenesis in NMO is humorally mediated, it is not unlikely that through epitope spreading, the immune response may broaden, thus eventually also being directed against epitopes located outside the optic nerves and spinal cord, therefore resulting in clear lesions affecting the brain and brainstem. It is of interest to note that half of the patients in the study by Pittcock et al., with a normal initial brain MRI, developed abnormalities on subsequent MRIs [3].

The recent finding of a disease-specific autoantibody, called NMO-IgG, supports the concept of a humorally mediated immune response [6]. Whether this autoantibody is pathogenic or merely an epiphenomenon is unknown. The fact that the antibody is directed against aquaporin-4, a water channel located in astrocytic foot processes at the blood–brain barrier throughout the entire central nervous system, suggests the latter [7,8].

Differentiating correctly between NMO and MS is clinically important, not only because of a difference in prognosis, but also from a therapeutic point of view. Several observations have suggested that immunosuppressive treatment modalities, including rituximab, are effective in NMO, whereas more ‘classic’ MS immunomodulatory drugs (e.g., interferon-beta and glatiramer acetate) are not, as was the case in our patient [1,9,10]. Therefore, based on our findings and those reported in the literature, we suggest that the third absolute criterion for the diagnosis NMO – no evidence of clinical disease outside the optic nerve or spinal cord – should be deleted from the diagnostic criteria, as has been suggested by others [3], and a stronger emphasis should be placed on the supportive criteria in order to differentiate the disorder from ‘typical’ MS.

References