

NEUROMYELITIS OPTICA

Brain abnormalities in a Brazilian cohort

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Abstract – Neuromyelitis optica (NMO) is a demyelinating disease consisting of relapsing-remitting optic neuritis and myelitis with a more severe course than Multiple Sclerosis. Recently, it has been shown that almost 50% of patients with NMO can have brain magnetic resonance imaging (MRI) abnormalities. We report on six Brazilian patients with NMO, fulfilling the 1999 Wingerchuck criteria for this disease, with abnormal brain MRI and discuss their clinical and radiological features.

KEY WORDS: neuromyelitis optica, brain abnormalities, MRI.

Neuromielite óptica: alterações encefálicas em pacientes brasileiros

Resumo – Neuromielite óptica (NMO) é doença desmielinizante, remitente-recorrente, com acometimento predominante dos nervos ópticos e medula espinal e uma evolução mais grave comparada à esclerose múltipla. Estudos recentes demonstraram que até 50% dos pacientes com NMO podem apresentar lesões encefálicas à ressonância magnética (RM). Relatamos seis pacientes brasileiros com NMO, que satisfazem os critérios diagnósticos de Wingerchuck (1999) para NMO, com alterações encefálicas em RM de encéfalo e discutimos seus dados clínicos e de imagem.

PALAVRAS-CHAVE: neuromielite óptica, alterações encefálicas, ressonância magnética.

Neuromyelitis optica (NMO), also known as Devic's syndrome or Devic's disease, is a demyelinating disease with predilection for the optic nerve and spinal cord^{1,2}. It was first considered to have a monophasic course and to be a multiple sclerosis (MS) variant, but data gathered in the past few years have shown NMO to be a relapsing disease with clinical behavior and pathology distinctive from MS^{1,3}. The first Brazilian reports on NMO have also disclosed extensive demyelination in the optic nerves and spinal cord^{4,5}.

The first attempt to establish diagnostic criteria for NMO demanded the occurrence of optic neuritis (uni or bilateral) and acute myelitis with no restriction on the timeframe over which the first attacks of optic neuritis and myelitis occur (index event), and no evidence of disease outside the optic nerve and spinal cord². Neurologists have thus been reluctant to diagnose NMO in someone with brain scan abnormalities, even though these abnormalities do not fulfill the criteria for MS⁶.

Therefore, we sought to survey our NMO patient's re-

cords in search of cases with brain MRI abnormalities and discuss their disease course.

METHOD

We retrospectively reviewed records of 63 patients attended at the Federal University of São Paulo Hospital Neuroimmunology Clinic, Brazil, from 1994 to 2006, who presented with a recurrent idiopathic demyelinating disease, predominantly affecting the optic nerves and spinal cord. Apart from the clinical course they had spinal cord lesions longer than three vertebral segments and brain magnetic resonance imaging (MRI) abnormalities not fulfilling MS criteria, thus meeting the 1999 criteria for NMO². Based solely on the records notes, 50% had some form of unspecific brain MRI abnormality. We selected six of these patients whose brain MRI were available for evaluation; we collected their clinical and radiological data respectively from medical records and from digital recordings of the Department of Radiology.

RESULTS

All patients were seen by at least one of the authors

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Table 1. Clinical and demographic features of patients with NMO and abnormal brain images.

Patient	Age of onset (years)	Sex	Etny	Disease duration (years)	Mean follow-up (years)	Time from 1 st symptom to index event (months)*	EDSS (1 st evaluation)	EDSS (last evaluation)	Relapse rate	Progression index
1	43	F	C	9	4	60	4.0	10	1.0	1.1
2	17	F	A	6	2	36	6.0	9.5	1.0	1.6
3	18	F	AB	5	4	5	6.0	6.5	1.2	1.3
4	24	F	C	3	3	3	4.0	4.5	1.3	1.5
5	20	M	C	1	1	2	4.0	9.5	5.0	9.5
6	23	M	C	7	7	1	4.0	4.0	2.5	0.6
Mean	24.2			5.2	3.5	17.8	Median 4.0	8.0	1.3	1.4

Relapse rate, relapses/years of disease; Progression index, EDSS/years of disease; F, female; M, male; C, Caucasian; AB, African-Brazilian; A, Asian.

Table 2. Sites of brain MRI abnormalities in our patients with Neuromyelitis Optica.

Patient	Spinal cord	Pons	Midbrain	Optic chiasm	Diencephalon	Internal capsule	Corpus callosum	Cerebral white matter
1	+	-	++	+	+	++	++	++
2	+	+	+	-	-	++	++	++
3	++	+	++	+	-	++	++	-
4	++	-	+	++	++	-	+	-
5	+	++ (MCP)	++	+	-	++	++	+
6	++	-	-	++	++	-	-	-

+, slight signal abnormalities; ++, expressive signal abnormalities; -, without signal abnormalities; MCP, middle cerebellar peduncles. Midbrain lesions were predominantly placed in the cerebral peduncles.

(Dr. Gabbai saw the patients on admission) up to 2006 with a mean follow-up of 3.5 years (range 1-7); their clinical information are shown on Table 1. Briefly, mean age at onset was 24.2 years (range 17-43), Kurtze's Expanded Disease Severity Score (EDSS) on first appointment was 4 (range 4-6) and evolved to 8 (range 4.0-10) on last visit, with a median relapse rate and progression index (last EDSS/disease duration)^{7,8} of 1.3 (range 1.0-5.0) and 1.4 (range 0.6-9.5) respectively. Four patients underwent cerebrospinal fluid (CSF) analysis, two had abnormal cell count (20 and 15/mm³) and the other two had normal cell count and absence of oligoclonal bands. Patients 3 and 6 responded to azathioprine plus prednisone and patient 4 improved after immunoglobulin therapy, and is currently on regular prednisone plus azathioprine maintenance therapy⁹. Patient 1 was refractory to all proposed treatments, including prednisone, methylprednisolone, azathioprine, cyclophosphamide, and immunoglobulin. Patients 2 and 5 had a very rapid course with severe disability, despite attempts to use different drug regimens, which included methylprednisolone, cyclophosphamide and azathioprine.

Brain MRI analysis revealed variable signal abnormalities in the spinal cord, concomitant to or extending from the cervical cord lesion in all patients (Figure). There were

signal abnormalities in the optic chiasm in all but patient 2 and in the diencephalon in three of them (Patients 1, 4 and 6) (Table 2). In patient 4, only slight abnormalities were observed in the midbrain and corpus callosum, whereas in patients 3 and 5 the lesions extended to the midbrain (predominantly to the cerebral peduncles), internal capsule and corpus callosum; patient 5 also showed a few focal signal abnormalities in the periventricular white matter. Patient 1 had the most striking brain involvement with extensive signal abnormalities in the periventricular white matter as well as in the right hippocampus. Patient 2 also had extensive subcortical white matter involvement with hypointense signal on T1-weighted images, suggesting early axonal loss. We observed a variable pattern regarding gadolinium enhancement: absence of enhancement (patient 3), mild punctiform enhancement (patients 4 and 6), corpus callosum enhancement only (patient 2) and nodular enhancement inside the lesions (patients 1 and 5). None of the images evaluated fulfilled the Barkhoff criteria for MS⁶.

Five patients had atypical symptoms (1, 2, 3, 4 and 6) including dysphonia, vomiting, hiccups, headache and altered mental status. Although patients 1 and 2 had longer time from the first relapse to index event, the sever-

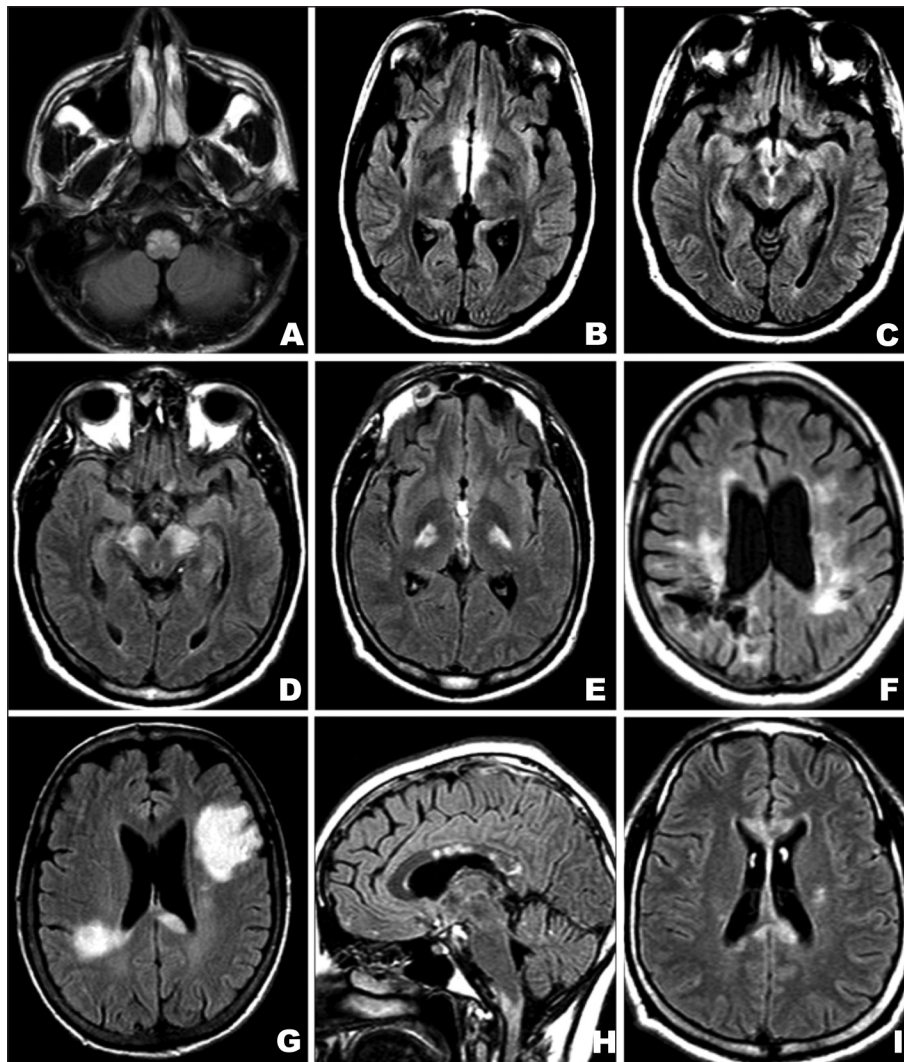


Figure. Brain lesion distribution in our patients with Neuromyelitis Optica. MRI FLAIR images. (A) medulla involvement (patient 6). (B, C) lesions in diencephalon and optic chiasm (patient 4). (D, E) signal abnormalities in middle cerebellar peduncles, midbrain and internal capsule (patient 5). (F) white matter abnormalities with cavitations suggesting early axonal loss (patient 2). (G) lesions in the periventricular and subcortical cerebral white matter and corpus callosum (patient 1). (H) corpus callosum, optic chiasm and medulla involvement (patient 3). (I) corpus callosum lesions and slight signal abnormalities in periventricular cerebral white matter (patient 5).

ity of their attacks and unresponsiveness to therapy was remarkable, and both needed respiratory support (Table 1). All patients had predominance of myelitis over optic neuritis attacks.

DISCUSSION

We report on a series of Brazilian NMO patients with brain abnormalities. Brain abnormalities in Brazilian patients with NMO have previously been reported^{10, 11}, as also in the original series from the Mayo Clinic², but until recently it was not known the cause of these lesions.

The identification of an antibody that binds to blood-brain-barrier (BBB) aquaporin 4 channel (NMO-IgG), which

is 73% sensitive and 91% specific^{12,13}, has turned NMO into a BBB channelopathy with abnormal humoral immunity activation. This antibody was positive in 68% of NMO patients with atypical brain lesions¹⁴ and in 63% patients with the optic-spinal MS¹⁵, which also had atypical brain lesion similar to the ones described by Pittock et al.¹⁴. Furthermore, sites of high brain aquaporin 4 expression seems to correspond to brain MRI lesions sites in patients with NMO¹⁶. The concept of an abnormal brain MRI in NMO has been recently evaluated in a cohort of sixty patients¹⁴ and led to new insights in disease aetiology and its diagnostic criteria¹⁷.

Our patients are younger and with higher EDSS scores

than the ones described by Pittock et al.¹⁴ and Nakashima et al.¹⁵. Three of them evolved to severe disability, including the need for respiratory support, which is in accordance with previous reports on the natural history of NMO^{1,18,19}. In the series reported by Pittock et al.¹⁴, almost half of the patients with brain MRI abnormalities had a normal scan on first evaluation, only disclosing brain abnormalities during follow-up images¹⁴. In our series, all patients but one presented with atypical brain MRI since the initial relapse, but they could not be classified as having MS. Only patient 1 showed extensive brain damage after five years of a relapsing-remitting optic-spinal disease. Possibly, other patients will develop brain lesions over time in a way similar to the ones described by Pittock et al.¹⁴; such evolution pattern should prompt neurologists to perform follow-up brain MRI in all NMO patients, regardless of their initial presentation. Testing for the NMO-Ig in our cohort would have reinforced the diagnosis of NMO^{12,13}, but this technique was unavailable in Brazil at time this patients were seen. At last follow-up visit one had died and 2 have reached an EDSS of 9.5 and have returned to their home town, thus making the serology testing not viable. However, due to the clinical presentation and the course of the disease, we are certain that these patients have recurrent NMO, despite their atypical pattern of brain lesions.

The impact of having or not lesions beyond the spinal cord and optic nerve in NMO patients is still uncertain. The pattern of lesion distribution in the brain is clearly different from what is seen in classical MS, but whether it means a more aggressive disease or late-stage Devic's disease, which all patients will reach, is difficult to determine without long-term epidemiological studies.

Treatment of NMO is a challenge since conventional MS therapy is not effective¹. The association of prednisone with azathioprine, plasma exchange and immunoglobulin seems to be beneficial^{9,20,21}, and rituximab was shown to be effective in a series of NMO patients and may be a treatment option²². However, it is yet unknown whether patients with brain lesions will respond differently to the available therapies.

In conclusion, abnormal brain MRI was once considered a distinctive feature of NMO. Nevertheless, recent data have shown that some patients may have brain MRI lesions which are not typical of MS. The question of whether NMO with brain abnormalities has a more aggressive course and will respond differently to proposed treat-

ments, or is simply the late stage of NMO, remains unanswered. The number of cases described so far and the lack of comparison to patients with normal brain MRI on follow-up prevent us from drawing further conclusions, and long-term studies are needed to answer these questions.

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