Optic neuromyelitis syndrome in Brazilian patients

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Objectives: To report the clinical features and outcome of 24 Brazilian patients with optic neuromyelitis syndrome (ONM); discuss the underlying pathological events associated with the ONM syndrome; review the nosological situation of ONM in the group of inflammatory and demyelinating diseases of the central nervous system.

Patients and Methods: Patients with ONM treated at the Hospital da Lagoa, Rio de Janeiro were studied. Demographic, clinical, magnetic resonance imaging, cerebrospinal fluid, and pathological data were analysed.

Results: The study consisted of 20 women, four men of whom 10 were white and 14 Afro-Brazilians. Clinical course was recurrent in 22 cases and monophasic in two. Neurological manifestations at inclusion were: sensory impairment (66%), bilateral (41.6%) or unilateral blindness (20.8%), paraplegia or quadriplegia (37.5%). The EDSS was moderate/severe in 70.8%. The underlying pathological events were respectively pulmonary tuberculosis and upper respiratory infection in the two monophasic cases; in the 22 recurrent ONM patients: pulmonary tuberculosis (3), neurocysticercosis (1), polyarteritis nodosa (1), antinuclear antibody and rheumatoid factor (1), antiphospholipid antibody primary syndrome (1), diabetes mellitus (1), hypothyroidism (1), and amenorrhea-galactorrhea (4). Normal cerebrospinal fluid was found in 52% and an inflammatory profile in 48%. Only four recurrent ONM white patients had brain and spinal cord magnetic resonance imaging and cerebrospinal fluid findings compatible with the diagnosis of multiple sclerosis. Large lesions were seen in 62% of spinal magnetic resonance images. Six of 12 recurrent ONM Afro-Brazilian died. There were no statistical differences in the demographic data of the two ethnic groups. Afro-Brazilians were significantly more severely impaired and had a higher mortality rate than the white patients.

Conclusion: These cases were classified as follows: two monophasic acute disseminated encephalomyelitis; one recurrent disseminated encephalomyelitis; three recurrent ONM associated with Hughes syndrome, autoantibodies and polyarteritis nodosa; six recurrent ONM with endocrinopathies; and finally, four multiple sclerosis cases. The remaining cases were not associated with any other condition. It would seem clear that ONM is a syndrome rather than a single disease.

Although there have not been many cases described as ONM in the medical literature, recent studies have provided sufficient important data to distinguish between MS and ONM. Unfortunately, cases of ONM with typical spinal cord T2 MR images of sausage shaped lesion extending over three cord segments, never seen in MS, combined with the classic changes of ADEM at necropsy, continue to be reported as MS despite strong evidence to the contrary.

The aim of this study is to define the nosological situation of ONM on the basis of the clinical, laboratory, and demographic features of 24 Brazilian patients with ONM, in order to determine if ONM, the Devic syndrome is a subtype of MS, a distinct disease, or a fragment of disseminated encephalomyelitis.

PATIENTS AND METHODS

Twenty four patients with the ONM syndrome treated at the Hospital da Lagoa, Rio de Janeiro in the period 1995–99 were selected from patients with demyelinating inflammatory diseases and included in this study. Their demographic, clinical, MRI, cerebrospinal fluid (CSF), and pathological features were analysed in relation to demyelinating events and associated

Abbreviations: MS, multiple sclerosis; ONM, optic neuromyelitis syndrome; RONM, recurrent optic neuromyelitis syndrome; ADEM, acute disseminated encephalomyelitis; RDEM, recurrent disseminated encephalomyelitis; TM, transverse myelitis; CSF, cerebrospinal fluid; MRI, magnetic resonance imaging; ON, optic neuromyelitis syndrome;
illnesses. Clinical analysis was also performed, based on the last follow up year 2001.

The inclusion criteria were: the occurrence of one or more bouts of ON and TM with no clinical evidence of other involvement of the CNS; normal MRI and CSF, or MRI and/or CSF findings clearly compatible with a demyelinating event.

A bout was defined as a neurological dysfunction lasting more than 24 hours. Remission was definite improvement of signs, symptoms or both that had been present for at least 24 hours, lasting at least one month to be considered significant.\(^1\) Bouts were classified as: unilateral or bilateral ON, TM complete (CTM) or partial (PTM), and as ONM when the clinical events ON and TM occurred simultaneously. Impairment and disability were rated according to Functional Systems (FS) and Expanded Disability Status Scale (EDSS).\(^2\)

All patients were given the following tests: standard haematological tests, antinuclear antibody, rheumatoid factor, thyroid tests, antithyroglobulin, thyroid microsomal, and antiphospholipid antibodies, HIV-1 and HTLV-I serology. Clinical and laboratory endocrinopathies and tuberculosis was also performed. Women patients were specifically asked about galactorrhoea and amenorrhoea unrelated to pregnancies. CSF was analysed in all patients: total and differential cell count, microbiological and fungal cultures. Albumin and IgG concentrations in serum and in CSF were determined by nephelometry. The extent and type of spinal cord MRI was observed in 16 patients (66 %), five with para-plegia and four with quadriplegia. The frequency of motor impairment was the same in the two ethnic groups but it was much more severe in the Afro-Brazilians (p=0.01). Sensory impairment was the same in the two ethnic groups but it was much more severe in the Afro-Brazilians (p=0.01). Sensory impairment occurred in 16 patients (66%), five of them with anaesthesia of the lower limbs up to a thoracic level, and of the entire body in one. Sphincter disturbances were noted in 14 of 24 patients, and double dose contrast CT scans were obtained for the other three. Brain MRIs were classified according to Paty et al\(^3\): I: strongly suggestive of MS, II: suggestive of MS, III: possible MS, IV: one lesion only, V: normal or other lesions. The extent and type of spinal cord MRI lesion were classified as follows: A1: large lesion (more than three segments) with cord swelling, A2: large lesion with cavitation, A3: severe atrophy, B: one small lesion, C: several small lesions, D: normal.

Demographic and clinical data were collected and analysed according to SIAPEM, the Brazilian database for MS.\(^4\) The \(\chi^2\) and Fisher's exact tests were done for dichotomous variables in Epi info 6. Necropsy was carried out on two patients.

### RESULTS

#### Demographic data

Twenty women and four men with ONM, 10 white and 14 Afro-Brazilian; 83% were born in the south eastern region of the country. The age at onset ranged from 14–55 years, mean 32.8 (10). There were no statistical differences in the demographic data of the two ethnic groups (see table 1).

#### Clinical course at inclusion

Monophasic in three patients (one white and two Afro-Brazilians) and recurrent (RONM) in 21. The number of bouts at inclusion were 104, with 1 to 12 bouts per patient, mean 4.3 (2.5); median 4.

#### Neurological impairment at inclusion

After a mean duration of disease of 7.7 (8.2) years, visual deficit was present in 20 patients: bilateral blindness in 10 (41% of all patients) and unilateral in six (20 %). A pyramidal syndrome was observed in 16 patients (66 %), five with paraplegia and four with quadriplegia. The frequency of motor impairment was the same in the two ethnic groups but it was much more severe in the Afro-Brazilians (p=0.01). Sensory impairment occurred in 16 patients (66%), five of them with anaesthesia of the lower limbs up to a thoracic level, and of the entire body in one. Sphincter disturbances were noted in 14 patients (58 %), six requiring permanent bladder catheterisation. Sensory (se), sphincter (sp), and visual (vi) impairment were also more frequent and more severe in the Afro-Brazilian group (FS-sensorial: p=0.005, p=0.01; FS-bowel and bladder: p=0.01, p=0.007; FS-visual: p=0.02 and p=0.01).

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### Table 1 Details of the 24 ONM Brazilian patients

<table>
<thead>
<tr>
<th>Patients</th>
<th>Gender</th>
<th>ETHNIA</th>
<th>Age at first bout</th>
<th>Time of disease</th>
<th>FS-PYR</th>
<th>FS-SENS</th>
<th>FS-BB</th>
<th>FS-VIS</th>
<th>EDSS</th>
<th>Follow up (2001)</th>
</tr>
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Time of disease FS-visual: p=0.02 and p=0.01).
EDSS at inclusion
Seven patients were mildly disabled (EDSS <3.5); seven moderately (EDSS 4–5.5), and 10 severely disabled (>6). Three patients were confined to wheelchair and six bedridden. Mild disability was more frequent in the white group (p=0.004) and severe disability in the Afro-Brazilian patients (p=0.007).

Follow up
The 24 ONM patients were prospectively studied (1995–2001) for one to five years. Patients with a monophasic course: case 1: only mild disabled 14 years after onset; case 21: blind but walks with unilateral support; case 11: an Afro-Brazilian woman had a new bout of unilateral ON after 20 months of disease, and was reclassified in the recurrent group.

The 22 RONM cases from 1995 to 2001 had a total of 51 new bouts, the EDSS scores increased in cases 3, 7, 11, 13, and 24, and six Afro-Brazilian women died (cases 2, 4, 5, 18, 21, 22). The time from onset to death ranged from eight months to 30 years, mean 11.4 (12.3). In all six cases death resulted from respiratory arrest during a severe bout of quadriplegia. Necropsy was performed in cases 4 and 18.

Table 2: Neurological manifestations of ONM syndrome

<table>
<thead>
<tr>
<th>ONM patients</th>
<th>Sex</th>
<th>Ethnicity</th>
<th>Number of bouts</th>
<th>Clinical course</th>
<th>First Myelitis</th>
<th>Index event 1</th>
<th>Index event 2</th>
<th>Index events 1, 2 interval</th>
<th>Bouts occurred between the index events 1 and 2</th>
<th>Bouts occurred after the second index event</th>
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<td>01 W</td>
<td>M</td>
<td>W</td>
<td>1 ONM</td>
<td>ONM</td>
<td>CMT</td>
<td>UON</td>
<td>40 days</td>
<td>CMT</td>
<td>BON+CTM</td>
<td></td>
</tr>
<tr>
<td>02 W</td>
<td>M</td>
<td>Afro</td>
<td>4 RONM</td>
<td>Optic</td>
<td>UON</td>
<td>CTM+UON</td>
<td>9 months</td>
<td>CTM</td>
<td>Optic+UON</td>
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</tr>
<tr>
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<td>Afro</td>
<td>5 RONM</td>
<td>Optic</td>
<td>UON</td>
<td>PTM+UON</td>
<td>24 months</td>
<td>PTM</td>
<td>Optic+UON</td>
<td></td>
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<tr>
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<td>M</td>
<td>Afro</td>
<td>8 RONM</td>
<td>Myelitis</td>
<td>CTM</td>
<td>UON</td>
<td>192 months</td>
<td>4 CTM</td>
<td>Optic+UON</td>
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<tr>
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<td>M</td>
<td>Afro</td>
<td>4 RONM</td>
<td>Optic</td>
<td>UON</td>
<td>CTM</td>
<td>24 months</td>
<td>Optic</td>
<td>CMT+Optic</td>
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<tr>
<td>06 W</td>
<td>M</td>
<td>Afro</td>
<td>3 RONM</td>
<td>Myelitis</td>
<td>CTM</td>
<td>UON</td>
<td>4 months</td>
<td>Optic</td>
<td>CMT+Optic</td>
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<tr>
<td>07 W</td>
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<td>Afro</td>
<td>7 RONM</td>
<td>ONM</td>
<td>PTM</td>
<td>UON</td>
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<tr>
<td>08 W</td>
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<td>3 RONM</td>
<td>Optic</td>
<td>UON</td>
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<td>36 months</td>
<td>UON</td>
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<tr>
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<td>Myelitis</td>
<td>CTU</td>
<td>UON</td>
<td>36 months</td>
<td>UON</td>
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<td>PTM</td>
<td>UON</td>
<td>45 days</td>
<td>PTM</td>
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</table>

CTM, complete transverse myelitis; PTM, partial transverse myelitis; UON, unilateral optic neuritis; BON, bilateral optic neuritis.

Optic nerve atrophy accounted for the permanent visual loss in 63% of the patients, unilateral in 21% and bilateral in 42%.

Neurological manifestations of the ONM syndrome
Clinical onset (first bout)
The initial manifestations of ONM syndrome were TM in nine cases (37.5%), ON in eight (33.3%), and simultaneous TM and ON in seven (29.2%), the diagnosis of ONM being possible at onset only in the last group. The interval between the two index events (ON and TM) in ONM bouts occurred from one to 45 days (mean:20 (17.5), median:20). After remission of a first TM bout, ON occurred after 4 to 192 months (mean:75.1 (70.9), median: 36). In the patients with ON at onset, a second event of spinal cord occurred after 4 to 240 months (mean: 56 (75.5) median: 29).

Table 3: Investigation of demyelinating diseases in 24 ONM Brazilian patients

<table>
<thead>
<tr>
<th>Method</th>
<th>Neuro image criteria</th>
<th>Number of patients</th>
<th>Results ONM patients</th>
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<td>Normal</td>
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<td>Cases 18, 22, 23</td>
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<tr>
<td>Brain MRI</td>
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<td>13</td>
<td>Cases 2, 4, 5, 6, 8, 10, 11, 12, 14, 16, 19, 20, 24</td>
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<td>Paty V – normal</td>
<td>13</td>
<td>Case 15: porencephalic frontal area</td>
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<td>Paty V – other diseases</td>
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<td>Case 21: large lesions at brain and brainstem – ADEM</td>
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<tr>
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<td>Paty IV – 1 lesion</td>
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<td>Cases 1 and 7</td>
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<td>Paty III – 2 lesions (1 periventricular)</td>
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<td>Paty III – 3 lesions or 2 lesions (1 periventricular)</td>
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<td>Cases 3, 9, 17</td>
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<tr>
<td></td>
<td>Paty I – 4 lesions or 3 lesions (1 periventricular)</td>
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</table>

Paty V, normal or other lesions; IV, one lesion only; III, possible MS; II, suggestive of MS; I, strongly suggestive of MS.

Bouts characteristics (table 2)
A total of 175 bouts were identified by anamnesis and from medical records (104 at inclusion and 51 at follow up): TM (56%), ON neuritis (24%) and ONM (18%). Myelitic bouts were more frequent in white patients (p=0.004) and ONM bouts in the Afro-Brazilian patients (p=0.007).
Prior and associated pathological events
In the two monophasic cases, the prior events were respectively pulmonary tuberculosis and upper respiratory infection, while in the RONM patients they were pulmonary tuberculosis (3), neurocysticercosis (1), polyarteritis nodosa (1), high levels of antinuclear antibody and rheumatoid factor (1), antiphospholipid antibody syndrome (1), diabetes mellitus (1), hypothyroidism (1), fever (1) and the amenorrhea-galactorrhea syndrome (4).

Neuroimaging and CSF findings
Brain MRI (table 3) was normal in 62% of 21 patients. Large demyelinating lesions typical of ADEM were found in the white matter of the parietal lobe, brain stem, and spinal cord of one ONM monophasic patient (case 21), who also had the diagnosis of pulmonary tuberculosis. Lesions suggestive of MS (Paty II or Paty I) were observed in four instances (19%).

Spinal cord MRI (table 4)
The most frequent finding consisted of large, T2 weighted areas of increased signal intensity (AISIs) more than three segments in length, central cavitation or severe atrophy (13 cases, 62%). Small T2 AISIs as seen in MS were found in four cases (19%). A normal cervical spinal cord MRI was found in two cases: in an ONM monophasic patient after a follow up of 10 years (case 1) and in a quadriplegic RONM after intravenous treatment with high doses of corticosteroids (case 22).

CSF findings
Fourteen CSF samples were normal (52%). There was pleocytosis in nine, only one with more than 50 cells, increased protein concentration in 11, blood-CSF barrier dysfunction in two of 18, high IgG index in one of 20, and oligoclonal bands in five of 23 instances. Subsequent CSF analysis during remission showed normalisation of both pleocytosis and protein content in four cases. Changes in CSF parameters during bouts and remissions are shown in table 5. There was a decrease of the inflammatory pattern during remissions.

Neuropathology
Postmortem examination was done in cases 18 and 4. Case 18 was a 25 year old Afro-Brazilian woman who died during her third bout, after eight months of disease. She was found to have pulmonary tuberculosis a few days before death. There was severe inflammatory damage of the spinal cord and optic nerves. The lesions consisted of destruction of the white matter with cavitation, many microglial cells and rare lymphocytes. The brain showed no macroscopic changes but microscopic study revealed small foci of demyelination in the corpus callosum and lower medulla. The second patient (case 4) was an Afro-Brazilian woman who died with nosocomial pneumonia after 30 years of recurrent ONM. Severe demyelinating lesions were found in the spinal cord and optic nerves. A brain MRI (fig 1) one week before death showed small lesions in the cerebral white matter (Paty II), without enhancement after contrast administration, that corresponded with the areas of demyelination found at necropsy (fig 1).
have clinical, MRI, CSF, and genetic data
Brazilian survey on MS confirm that Brazilian MS patients
features. Recent data from the South Atlantic Project, a
(RRMS) on the basis of demographic, clinical, MRI, and CSF
syndrome should only rarely be included as cases of MS.

These patients improved from their bouts, which consisted of myelitis with predominantly sensory
impairment and mild unilateral visual impairment. They were
only mildly disabled after follow up of 6, 5, 17, and 11 years.

On the other hand, only 29.2% of the MS patients in the SIA-
population, the disease was most prevalent in young white
women. RRMS was present in 89% and a primary progressive
disease in 11%; the EDSS scores in the RRMS group showed
mild disability in 70%, moderate in 9.8%, and severe in 19.9%
of the patients after a mean duration of disease of seven years.

We found pleocytosis of more than 50 cells/mm³ in only 4% of our CSF analyses, and
protein concentration higher than 70 mg/dl in only 15%.

Another important clinical difference between Brazilian
RRMS and ONM Brazilian patients is the degree of im-
pairment and disability on follow up. There is a statistically sig-
nificant difference between the EDSS and the FS scores: higher
impairment and more disability in the ONM group (fig 3).

The pathological features and the MRI can be helpful in
differentiating ONM from MS. Necropsies of five ONM
patients reported by Mandler et al demonstrated extensive,
severe necrotising myelopathy, with thickening of blood
d blood vessels but without lymphocytic infiltrates and prominent
necrosis of gray and white matter with cavitation, affecting
only the optic nerves and the spinal cord. The authors empha-
sised the importance of a normal brain MRI in the in vivo
diagnosis of ONM.

Brain images, which were normal at disease onset, may
show demyelinating lesions after long evolution as exempli-
ified by case 4. MRI extension of the cervical lesions into the
brain stem occurred in cases 5, 11, and 12 like those noted by
Wingerchuk et al. One such example is case 11, a 25 year old
Afro-Brazilian woman with fever, malaise, galactorrhea, and
amenorrhea, who developed urinary retention followed by
subacute quadriaparesis and bilateral optic papillitis with
unilateral loss of vision. During the acute phase, she exhibited
bulbar signs (deviation of the tongue and hiccups), and MRI

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Figure 3 Comparison of impairment and disability
(FS/EDSS/KURTZKE) between Brazilian multiple sclerosis patients
with relapsing remitting course and ONM patients
(A) Disability by EDSS: RRMS—447 Brazilian patients—South
Atlantic project. ONM—20 ONM Brazilian patients [excluded
ONM/MS patients—cases 3, 9, 13, 17]; (B) Impairment by FS:
RRMS—447 Brazilian patients—South Atlantic project. ONM—20
ONM Brazilian patients (excluded ONM/MS patients-cases 3, 9,
13, 17).

be in accordance with previous reports of the high numbers of
non-white cases of Devic’s syndrome in the United
Kingdom, the United States, and Martinique.

There were important differences in the CSF findings
between our ONM patients and those with definite MS: mild
pleocytosis and increased CSF protein content were more
common in ONM and increased IgG indices and oligoclonal
bands, which occurred in 85% of the clinical definite MS Bra-
zilian patients, were very rare. Compared with MS where the
CSF changes are independent of the activity of the disease, in
ONM all the CSF abnormalities (pleocytosis, high level of pro-
tein, high IgG index, and oligoclonal bands) disappeared dur-
ing remission in the majority of the cases. In contrast with the
study on ONM by Wingerchuk et al, we found pleocytosis of
more than 50 cells/mm³ in only 4% of our CSF analyses, and
protein concentration higher than 70 mg/dl in only 15%.

The striking characteristic of our series of 24 Brazilian ONM
patients is the relapsing remitting clinical course. Despite the
superficial resemblance to MS, only four of the 22 relapsing
ONM patients could be classified as clinically definite MS
(cases 3, 9, 13, 17). The four were all white women
with more than two years between events and serial brain
MRIs showing Paty I and II involvement of the brain as well as
small spinal cord lesions (fig 2: case 9). Two had CSF
oligoclonal bands but isoelectric focusing of CSF was not done
in the other two. These patients improved from their bouts,
which consisted of myelitis with predominantly sensory
symptoms and mild unilateral visual impairment. They were
only mildly disabled after follow up of 6, 5, 17, and 11 years.

Only case 3 had a mild bout of ONM. These data support the
proposition that the majority of patients with Devic’s syndrome should only rarely be included as cases of MS.

RNMO must be differentiated from relapsing remitting MS
(RRMS) on the basis of demographic, clinical, MRI, and CSF
features. Recent data from the South Atlantic Project, a
Brazilian survey on MS confirm that Brazilian MS patients
have clinical, MRI, CSF, and genetic data that are quite
similar to the “western type” of MS. Demographic data indicated that in Brazilians, a highly ethnically diversified
population, the disease was most prevalent in young white
women. RRMS was present in 89% and a primary progressive
disease in 11%; the EDSS scores in the RRMS group showed
mild disability in 70%, moderate in 9.8%, and severe in 19.9%
of the patients after a mean duration of disease of seven years.

On the other hand, only 29.2% of the MS patients in the SIA-
PEM database are Afro-Brazilians (black or mulatto) as com-
pared with 70.8% of the 20 ONM patients. This would seem to

DISCUSSION

The pathological features and the MRI can be helpful in
differentiating ONM from MS. Necropsies of five ONM
patients reported by Mandler et al demonstrated extensive,
severe necrotising myelopathy, with thickening of blood
d blood vessels but without lymphocytic infiltrates and prominent
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unilateral loss of vision. During the acute phase, she exhibited
bulbar signs (deviation of the tongue and hiccups), and MRI

Figure 2 Case 9 (ONM/MS patient) MRI showing small
periventricular T2 images (Paty II) and small spinal cord lesions.
showed a large cervical lesion extending into the medulla oblonga (fig 4).

Monophasic Devic’s syndrome probably represents a fragment of acute disseminated encephalomyelitis (ADEM). Our two monophasic ONM patients had a previous history of infectious diseases: an acute respiratory infection (case 1) and pulmonary tuberculosis (case 21). The diagnosis of ADEM in this 48 year old Afro-Brazilian was confirmed by the presence of large brain and spinal cord lesions in MRI images (fig 5). We also found evidence of active pulmonary tuberculosis (by chest radiograph, sputum analysis, and bronchoscopy) in RONM cases 4 and 6. Sporadic reports of patients with ONM in association with pulmonary tuberculosis have been published: Silber et al described eight patients, with severe disease and poor neurological recovery. The failure to demonstrate mycobacterium in the CSF or in the CNS at necropsy suggests that the ONM results from an immune reaction triggered by a specific antigenic stimulus. In many cases of ADEM the preceding infection may be very mild so that it is not mentioned, or has been forgotten, or was actually subclinical and unrecognized. It is also well known that prior vaccinations are often not mentioned by the patient, or not asked about by the doctor, especially as there is so much emphasis by public health authorities that vaccines are perfectly safe and do not cause ADEM.

Recurrences of bouts of neurological dysfunction have almost invariably been ascribed to MS but such events also can be seen in recurrent (RDEM) and multiphasic disseminated encephalomyelitis (MDEM). In RDEM the first, acute bout is followed by one or more episodes that reproduce all or some of the symptoms of the original episode; this symptomatic stereotype that is quite rare in MS, can be seen in some cases of RONM. Our case 7 is a good illustration of this type of illness: a 55 year old Afro-Brazilian woman was treated with praziquantel for cerebral cysticercosis one year before the onset of RONM. She developed a subacute episode of TM at the T4 level and partial bilateral visual loss, with complete remission after corticotherapy. This first episode was then followed by seven episodes in the subsequent eight years, each one reproducing all or some of the symptoms of the original attack, mimicking the description of RDEM. Brain MRI revealed only one small periventricular lesion (Faty IV). A small enhancing demyelinating lesion was seen at the T4 level and extensive spinal cord atrophy was demonstrated after eight years of disease.

A special group of RONM cases associated with endocrinopathies was first described by Vernant et al. The first Brazilian report of this new syndrome was published in 1999 and is case 16 in this series: a 44 year old black woman had three episodes of ONM in a 14 year period, one of them associated with amenorrhea and galactorrhea. Cervical spinal cord MRI showed a large lesion with syringomyelic cavitation, but normal brain images. Three more Afro-Brazilian women, and one white woman in our series have also developed endocrine disturbances: amenorrhea-galactorrhea (cases 7 and 11), hypothyroidism (case 5), and diabetes mellitus (case 20), associated with severe motor and visual deficits, large spinal cord lesions and normal brain MRIs. Interestingly, a ONM-MS case (9), also had galactorrhea and amenorrhea with an increased prolactin level before and after the third bout, which disappeared after corticotherapy.

We have also found ONM to be associated with connective tissue disorders: a 39 year old white woman (case 15)
presented with sudden loss of vision and papillitis in the left eye. She failed to respond to treatment with methylprednisolone. Six months later, she complained of acute pain in the right eye, followed by loss of vision rendering her completely blind. Two years afterwards she developed paraplegia with a T10 sensory level, also without recovery. Spinal cord MRI showed a large lesion of the thoracic spinal cord. Polyradiculitis nodosa had been diagnosed 10 years before, when she was found to have severe hypertension, peripheral neuropathy, joint pains, fever, and hair loss. Nerve biopsy revealed vasculitis. Anticardiolipin antibodies were not present. The patient had been treated for lung tuberculo-
sis at the age of 18.

ONM and the Hughes syndrome was detected in case 10: a 43 year old Afro-Brazilian from northern Brazil, complained of progressive paraesthesia of the legs ascending to the T2 level and involving his arms, hands and face. Forty five days later he lost the vision of the right eye and developed urinary urgency, constipation, and leg weakness. Brain MRI was normal but a large, enhancing MRI demyelinating lesions extending from C3 to C6, and from T5 to T9 were found. His CSF had an inflammatory profile with increased IgG and oligoclonal bands identified in repeated tests. After suffering four bouts of ONM in four years he is almost blind in both eyes, has no motor impairment, and only slight sensory symptoms. The diagnosis of primary antiphospholipid syndrome (Hughes syndrome) was based on high levels of antiphospholipid IgG in two samples (70 U and 57 U). The presence of anticardiolipin antibodies has been reported in patients with both MS and with ONM. Twenty per cent of 100 MS patients had high levels of anticardiolipin antibodies (>10 U) fulfilling the diagnostic criteria for primary antiphospholipid antibodies syndrome. It has not yet been established if the neurological manifestations of Hughes syndrome can be distinguished from MS or ONM, or whether these cases constitute a novel nosological entity. The associations of ONM with connective tissue disorders, antiphospholipid and autoantibodies, vaccination, infectious diseases, including pulmonary tuberculosis, neurocysticercosis, and viral diseases, suggest that a B cell mediated immunopathogenic mechanism may play an important part in the pathogenesis of the ONM syndrome.

Conclusions
Our results are in agreement with the Mayo Clinic study that discarded the general idea that monophasic severe bilateral ON and TM occurring within a brief time interval is essential for the diagnosis of ONM. Indeed, only one of our patients met that criterion. Our series of patients with ONM consisted of two monophasic cases of ADEM, one of RDEM, one case each of RONM associated with antiphospholipid antibodies, autoantibodies, and polyarthritis nodosa, and six cases of RONM with endocrinopathies. Four cases were diagnosed as definite MS. Finally, eight ONM cases with recurrent course, the disease affected only the CNS system with no evidence of other associated disease.

ONM patients had more severe impairment and disability when compared with Brazilian RRMS patients of the South Atlantic Project, and Afro-Brazilian patients with RONM had a worse prognosis with high morbidity and mortality. We can infer from our series that ONM is a syndrome rather than a single disease, and suggest that the term Devic's disease should be abandoned. It is clear that a number of conditions are associated, or result in ONM, and that the common prac-
tice of including such cases as variants of MS is inappropriate as only four, one sixth of our cases, qualified as such. Further-
more, it is noteworthy that 12 of our patients had what one might describe as fragments of one or another form of disseminated encephalomyelitis.

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