



# Atypical Demyelinating Disorders Suggesting Multiple Sclerosis

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**Objective :** We present two patients with clinical course, MRI findings, electrophysiologic studies, and brain biopsy not suggestive of any previously described demyelinating disorder.

**Materials and Method :** One with history of optic neuritis became comatose in a steady pattern within 3.5 months and died. The other who developed left hemiplegia showed multiple ring-enhanced nodular lesions in MRI and good response to steroid and azothioprine.

**Discussion :** The assesment of the patient suspected of having MS remains a clinical challenge in which sound judgement is of paramount importance. The diagnosis was established by the clinical course, the neuroradiological findings, and the result of brain biopsy.

**Conclusion :** We suggest that several steps should be followed by a neurologist when first confronted by a patient suspected of having Multiple Sclerosis.

**Key Words :** Atypical, Demyelinating Disease, Multiple Sclerosis

## Multipl Sklerozu Düşündüren Atipik Demiyelinizan Hastalıklar

**Amaç :** Klinik tablo, MRG bulguları, elektrofizyolojik çalışmalar ve beyin biyopsisi daha önce tariflenen demiyelinizan hastalıkları düşündürmeyen iki hastayı sunduk.

**Materyal ve Metod :** İlk hastamız optic nörit tablosunu takibeden 3.5 aylık süreç sonunda bilinç kaybı ve koma tabloları sonrası kaybedildi. Sol hemipleji nedeniyle gelen diğer hastanın MRG'sinde çok sayıda çevresi kontrast tutan nodüler lezyon gözlenmiş, steroid ve azotioprin tedavisi ile rahatlamıştı.

**Tartışma :** MS şüphesi ile değerlendirilen hastalarda klinik tanı gayret gerektirmektedir. Daha önceki bilgilere bağlı önseziler halen en önemli bölümü oluşturmaktadır. Tanı klinik seyir, nöroradyolojik bulgular ve beyin biyopsisi ile konur.

**Sonuç :** MS şüphesi ile değerlendirilen hastalarla karşılaşıldığında nörologlar tarafından değişik basamakların takibini önermekteyiz.

**Anahtar Kelimeler :** Atipik, Demiyelinizan Hastalık, Multipl Skleroz

Multiple Sclerosis symptoms arise from disease affecting the optic nerves, pyramidal tracts and sensory nerve pathways. For a clinical diagnosis of multiple sclerosis (MS) there must be evidence of CNS white matter lesions and differential diagnosis must be excluded.

## CASE REPORTS

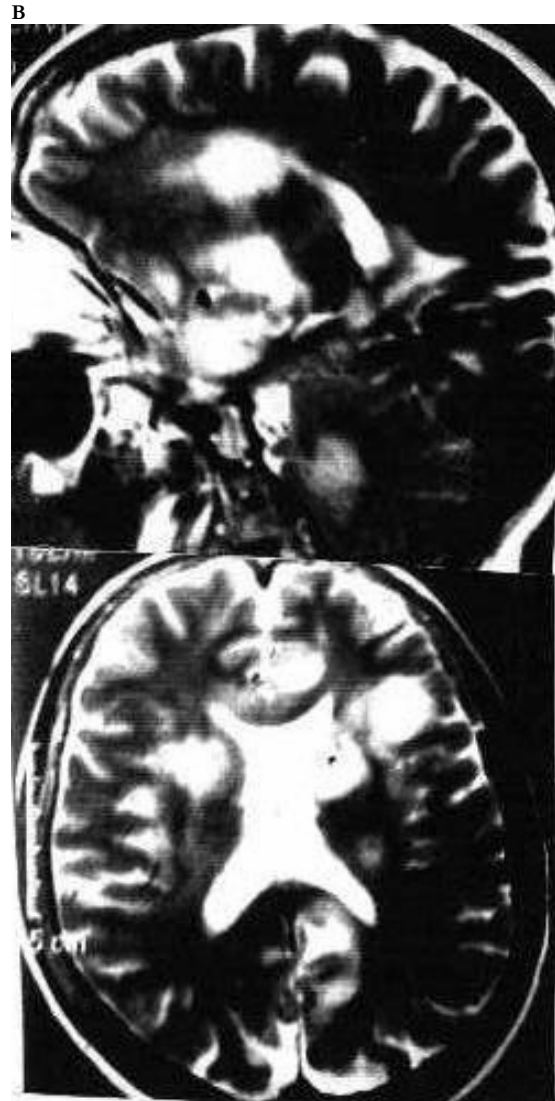
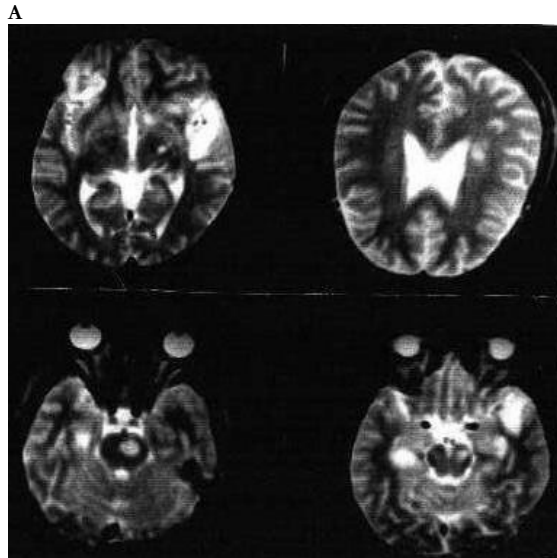
### Case 1

A 55 year-old woman developed numbness and burning feelings in the right side. There was no other pathology except for disappearance of right nasolabial sulcus in neurologic examination and temporal pallor in the left eye funduscopy. She had a history of zona infection followed by optic neuritis (papillitis) three months ago. Fifteen days after admission, right hemiparesis developed. In a steady pattern, cerebellar, myelopathic and mental symptoms progressed. Right hemiplegia, left hemiparesis, left homonymous hemianopsia, dysphagia, memory and cognitive impairment, right sided hypoesthesia developed. She died at the end of 3.5 months. Erythrocyte sedimentation rate (ESR) was 26 mm/hour. All the relevant serum biochemical tests including anti-phospholipids, complements,

cryoglobulins, Lyme antibody, anti-HIV, anti-HBs, immunoglobulins, autoantibodies and ANCA were found to be normal. Cranial CT of case-1 showed diffusely involved hypodense lesions in both cerebral hemispheres and cerebellum. There was little enhancement. The lesions were more prominent in later CT scan. Magnetic resonance imaging (MRI) scans obtained in optic neuritis (ON) period and later showed several lesions of high signal intensity on T2-weighted images within the brain stem, corpus callosum, basal ganglia, cerebellum and subcortical white matter. Some of the lesions in the former MRI scan disappeared while new and extensive lesions appeared in the later. (Picture 1) There were mildly increased protein (65 mg/dl), lymphocytic pleocytosis (100/mm<sup>3</sup>) and no oligoclonal bands in CSF examination. Visual evoked potentials in the left eye showed prolonged P100 wave latencies. EEG demonstrated diffuse slowing.

Infectious demyelinating diseases especially progressive multifocal leukoencephalopathy, arteriolosclerosis, inflammatory vasculitis, Schilder's disease were thought for the differential diagnosis. The patient was administered intravenous steroid therapy. Stereotactic biopsy was performed. Histopathological examination showed demyelinating disease suggesting multiple sclerosis. A diagnosis of secondary progressive multiple sclerosis was made depending upon a history of optic neuritis, a subsequent remission period, clinical manifestations, and brain biopsy.

**Figure 1.** MRI scans obtained optic neuritis period (A) and latter (B) showed high intensity lesions on T2 weighted images within brain stem, corpus callosum, cerebellum and subcortical white matter.



### Case 2

A 38-year-old woman presented with a 1-week history of difficulties affecting the left side of body. She became aware that the left arm was clumsy. Over the following 15 days we noticed increasing weakness of her left arm and leg. Left hemiplegia developed. She had a history of poliomyelitis so that her right leg was shorter and thinner. She had no risk factor for atherosclerosis. Examination revealed left hemiplegia and extensor plantar responses bilaterally. There was severe involvement of pyramidal pathways on the left side of the body. There was no cranial-nerve dysfunction. Deep sensations were severely decreased especially on the left side of body. Fundoscopic examination was normal. There was no vision loss. ESR was normal (17 mm/hour). There was no abnormality in blood tests. Antibodies related

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to inflammatory-demyelinating disorders was negative. Brain CT examination showed bilateral hypodense lesions in centrum semiovale. MRI revealed multiple ring-enhanced nodular lesions that were hypointense in T1-weighted images, and hyperintense in T2-weighted images. There was mass effect and edema around lesion located in the periventricular white matter of right side. Oligoclonal band was positive in both serum and CSF examination. Mildly elevated protein (62 mg/dl) was seen in CSF. Because of atypical MRI lesions MR spectroscopy examination was performed. Decreased N-Acetyl Aspartate peak, increased lactate and choline peaks were seen. There was minimal increase of myoinositol peak. There was no correlation between clinical and paraclinical findings. She was diagnosed as having a demyelinating disorder and steroid treatment was started. Although steroid pulse therapy for ten days, left hemiplegia was developed. Azothioprine was added to treatment. After one week regression was seen. No change of lesions were seen in later MRI. When the patient was admitted home, left hemiparesis (prominent on the upper extremities, 3/5 in motor power) was seen in clinical examination. Plantar reflex was extensor on the left side. There was no change of other examination findings. In the following weeks under monthly immunosuppressive therapy, motor functions improved (4/5 in motor power).

**Picture 2.** In case-2, brain CT shows rounded subcortical hypodense lesion but no concentric pattern (A); MRI shows ring-like lesions of demyelination and some lesions produces mass effect (B).



## DISCUSSION

The diagnosis of MS is fundamentally clinical. In modern trials, paraclinical evidence should be used with Poser's criteria. There are a number of diseases that exhibit typical MS lesions on MRI and oligoclonal bands in CSF examination. Many conditions can produce a multifocal central nervous system relapsing/remitting course in adults and problems in diagnosis may arise when there is a polysymptomatic and multiphasic presentation.<sup>1,2</sup> No clinical feature is exclusive to one or the other disorder.

MRI and CSF findings were not typical with subcortical involvement and negative oligoclonal band respectively in case-1, so diseases mimicking MS clinically with both MRI and CSF criteria were all considered in differential diagnosis. Was it an MS attack triggered by antecedent infections, as were acute disseminated encephalomyelitis (ADEM)? Was it multiphasic ADEM? Was it fulminant MS simulating progressive multifocal leukoencephalopathy (PML)? Was it PML with no predisposing condition? Was it a virus related neurological deterioration remote from zona and resembled PML?<sup>3,4</sup>

MS may be steadily progressive and be with atypical paraclinical findings in older ages.<sup>1,2</sup> She was older aged and had a fulminant form than expected for MS so case-1 seems to be clinically definite MS with optic neuritis, remission period and involvement of tracts. Progression was seen after she had remission followed optic neuritis, so acute Marburg variant was not thought.

ON is usually a first manifestation of MS. Short-term follow-up studies showed that patients presenting with ON who have lesions on MRI frequently develop a clinically definite MS and papillitis treated by steroid or remission period after steroid treatment

signs to MS.<sup>5,6,7</sup> Similar presentation and ON with remitting period were seen in case-1 so MS diagnosis was made.

A few patients with clinically definite MS have no oligoclonal band that should cast doubt on the diagnosis.<sup>8,9</sup> Patients with no oligoclonal bands in their CSF were older aged and had experienced their first symptoms at a later age, and suffered more often from the chronic progressive form of the disease.<sup>1,10</sup> ON patients without oligoclonal bands also develop dissemination. Lymphocytic pleocytosis ( $>50 / \text{mm}^3$ ) should concern about diagnosis and shows severity.<sup>8</sup> In case-1 who was 55 years old, there was lymphocytic pleocytosis ( $100 / \text{mm}^3$ ) but no oligoclonal band in CSF. She showed very severe disease presentation. She died at the end of nearly seven months. For case-2 who was obvious laboratory supported definite MS, oligoclonal band was positive and it was a strong factor against the diagnosis of Balo's disease.

MRI abnormalities are characteristics, although they are not specific to MS. All white matter is susceptible but typical sites for plaques include the spinal cord, medulla, pons, cerebellar white matter, optic nerves and corpus callosum. 40% of plaques occur in the periventricular white matter. Presence of lesions in the corpus callosum is almost surely related to multiple sclerosis.<sup>11,12</sup> Grey matter can be rarely involved.<sup>13</sup> On a proton density and T2 weighted scan, MS lesions appear as very bright white areas. Four or more lesions in the white matter at onset of symptoms is strongly suggestive of MS. MRIs of case-1 revealed several lesions of high signal intensity on T2-weighted images within the brain stem, corpus callosum, basal ganglia, subcortical white matter especially U-fibers and cerebellum. These lesions were iso- or hyperintense relative to brain on T2-weighted images. Some of these lesions in the former MRI scan disappeared while new and more numerous lesions appeared in the later which were obtained 13 weeks after optic neuritis attack. (Picture 1) The places and characteristics of some lesions on MRI were unusual for MS and there was extensive disease involving the corpus callosum and adjacent white matter even subcortical part. The combination of gadolinium-enhancing lesions and non-enhancing T2-lesions increased the likelihood of early progression in case-1.<sup>14</sup> Also we know that there is an overall correlation between MRI and disease severity. Patients with chronic progressive form and lots of lesions usually have a much severe disease like case-1.<sup>13,15</sup>

Case-2 seemed to be Balo with imagings. (Picture 2) But the clinic was stable and there was a very good response to steroid therapy. In concentric sclerosis, a brain CT scan shows rounded bilateral subcortical frontoparietal hypodense zones with peripheral contrast material enhancement.<sup>12,16</sup> MRI shows concentric lesions better than CT scan. Serial MRI studies allow us to observe the development of concentric structures.<sup>12,14,16</sup> There are some reports of MS with concentric lesions and it is known that Balo's disease may not have a fulminant course as described in the past and MR appearance of the lesions may resemble that of an MS plaque.<sup>17,18</sup> Another common radiologic feature in MS is the lack of mass effect or edema in the surrounding white matter, even in large lesions. Acute lesions can be quite large and can produce a mass effect.<sup>19,20,21</sup>

In literature there is a case reported with multiple ring-like lesions of demyelination in which Balo's disease diagnosis was made on the base of brain MRI and stereotactic biopsy. MRI spectroscopy (MRS) was carried out 2 months after the onset and the MRS of that case in literature showed a decreased N-Acetyl-Aspartate peak, an increased Choline peak, presence of large lipid peaks and an increase in myoinositol peak.<sup>19</sup> CT scan of brain in our case-2 demonstrated hypodense lesion but no concentric pattern. Concentric lesion seen on MRI was quite large and had an edema around it. MRI's of case-2 demonstrated a decreased N-Acetyl-Aspartate peak, an increased Choline peak, and an increase in myoinositol peak. These findings are similar to previous cases of MS reported.

Cerebral biopsy is advised in selected clinical cases with serious worsening of the clinical condition in the absence of any other diagnostic clue. As with inflammation, demyelination and remyelination occurs to varying degrees depending on the form and stage of MS. Perivascular inflammatory cells accumulation and glial scar tissue formation around the demyelinated axons are seen in early MS.<sup>13</sup> In contrast to early MS, the plaques of late (chronic) MS show extensive oligodendrocyte loss. Astrocyte activation may be seen in late MS, often occurring simultaneously with active demyelination.<sup>13,22</sup> Other features of chronic MS include marked brain atrophy, extensive demyelination, loss of axons, gliotic scars and lymphatic-vessel like structures in perivascular connective tissue spaces.<sup>13,23,24</sup> The inflammation is more pronounced in chronic MS and demyelination is accompanied by extensive destruction of oligodendrocytes. An acute fulminant

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phase may occur as the terminal event of chronic MS.<sup>13,23,25-27</sup> The brain biopsy of case-1 showed perivascular lymphocytic infiltration, multiple axonal edemas, astrogliosis, myelinoclasia, intercellular eosinophilic granules, and reactive astrocytes. There was no inflammatory response and those pathologic lesions were thought to be chronic in nature.

Clinical symptoms and signs in MS are called by demyelination, edema, toxic mediators and loss of axons. Those induced by edema or toxic mediators (both due to inflammation) resolve rapidly after the onset of corticosteroid therapy. Kato et al report a case with Balo's disease. Dexamethasone was given intravenously, the clinical manifestations were resolved within 2 weeks. The MRI findings of case reported by Murakami were markedly improved after 3 weeks.<sup>28,29</sup> In case-2, following the initiation of steroid and immunosuppressive therapy, she showed remarkable clinical improvement.

*In conclusion*, the assessment of the patient suspected of having MS remains a clinical challenge in which sound judgement is of paramount importance. We reported two atypical cases suggestive of MS. In case-1, the diagnosis was established by the clinical course, the neuroradiological findings, and the result of brain biopsy. For second case, it was obvious laboratory supported definite MS but MRI findings were unusual. Oligoclonal band was positive and it was a strong factor against the diagnosis of Balo's disease. In addition to CSF findings, good response to steroid and immunosuppressive therapy has also been described in MS as case-2. We need to perform biopsy for definitive diagnosis of case-2.

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