Marburg Variant Multiple Sclerosis

Radomír Taláb, Zdeněk Kundrata

Department of Neurology, Medical Faculty, Charles University and University Hospital in Hradec Králové, Czech Republic

Correspondence to: Radomir Talab, MD., PhD.
Department of Neurology, Medical Faculty,
Charles University and University Hospital in Hradec Králové,
Sokolská 581, 50005 Hradec Králové, Czech Republic.
TEL: +420 495 835 233; FAX: +420 495 835 204; E-MAIL: radomir.talab@gmail.com

Submitted: 2011-05-05 Accepted: 2011-06-16 Published online: 2011-08-29

Key words: **multiple sclerosis; Marburg variant; acute disseminated encephalomyelitis; Schilder disease; Baló disease; magnetic resonance imaging**

Neuroendocrinol Lett 2011; **32**(4):415–420 **PMID:** 21876497 NEL320411C04

Abstract

In this case report we describe the case of a 24 year-old female with a fulminant demyelinating disease of white matter. Disease progression was most probably consistent with the Marburg variant (malignant form) of multiple sclerosis with rapid deterioration of the patient's clinical condition, including bulbar symptoms and epileptic paroxysms and ending with persistent coma and tetraparesis, over the course of 6 months from first symptoms. Repeated Magnetic Resonance Imaging (MRI) examination showed progression of multiple demyelinating lesions culminating in a contiguous focal disorder of the white matter extending both supratentorially and infratentorially. The serial MRI changes closely mapped the deterioration in the patients clinical status. Our patient showed no response to repeated pulse corticotherapy, administration of intravenous immunoglobulins, serial plasmapheresis, and combined high-dose pulse immunosuppression (specifiy what was used here) and mitoxantrone.

CASE REPORT

INTRODUCTION

Multiple sclerosis (MS) is a chronic autoimmune demyelinating disease of the central nervous system. It can be counted among the most frequent causes of disability in young adults. In 85% of cases, the disease begins with the relapsing-remitting form, where acute periods of neurological symptoms alternate with remissions. In 30 to 40% of these patients, the disease develops into the secondary chronic progressive phase during the first ten years (Weinshenker *et al.* 1989). The relapsing-progressive multiple sclerosis is characterized by an increase in neurological deficits even between the individual relapses. The primary chronic progressive form affects 10 to 15% of patients, and is characterized by an unrelenting progression in neurological deficits. In addition to these 'classical' forms, numerous reports also describe borderline forms of the disease. These include the tumefactive demyelinating lesions (so-called Baló, Marburg and Schilder forms), demographic variants (MS onset in the young and elderly), and related disorders (neuromyelitis optica and acute demyelinating encephalomyelitis) (De Seze 2006). In the more rare forms, which are malignant both in severity and in course, the disease manifests by a rapid increase in neurological deficits, most likely caused by failure of suppressor mechanisms and by extensive damage to axons and oligodendrocytes in the lesions (Havrdová *et al.* 2001). In particular, the Marburg variant of multiple sclerosis belongs to the group of idiopathic inflammatory-demyelinating diseases (IIDDs). This uncommon

acute fulminant form of MS is characterized by massive demyelination of white matter, a monophasic course and rapid progression (Blumhardt 2004; Canellas *et al.* 2007). Although seldom encountered in routine practice, these rare variants are important as they often arise in the differential diagnosis for severe, acute demyelinating disease, including MS and acute disseminated encephalomyelitis (ADEM) (Simon & Kleinschmidt-DeMasters 2008; Bastianello *et al.* 2004; Pichiecchio *et al.* 2009). The outcome is usually dismal with death due to involvement of the brain stem with bulbar paralysis. The initially small, focal demyelinating lesions coalesce into large plaques in the white matter (Lisa & Lisy 2007). The pathophysiology is identical to that of MS.

MS is an autoimmune disease in which the myelin sheath of the central nervous system (CNS) is degraded, resulting in reduced cationic nature of the 18.5 kDa isoform of myelin basic protein (MBP). In rare cases of acute, fulminant Marburg variant MS, MBP is even less cationic compared to MBP from both normal, and chronically MS-afflicted individuals (Johnson *et al.* 1990). This observation was made based on electron microscope examination in vitro. In addition, the less positively charged active isomer of MBP was found to form longer protein-fat complexes compared to those in healthy individuals and patients with chronic MS. This finding may correlate with the chemical modifications of MBP in living tissues and contribute to the structural instabilities of myelin with subsequent antigen presentation of this modified protein (Beniac *et al.* 1999).

Magnetic resonance imaging (MRI) plays a key role in the diagnosis of demyelinating disorders of the central nervous system (CNS), as it has high resolution capability and is to reveal even minor pathological lesions brain tissue. MRI has high sensitivity in the diagnosis of multiple sclerosis (approx 90%) but the specificity is lower, less than 75% (Chong 2004). Predilection areas of MS include the corpus callosum, periventricular and juxtacortical white matter. Other areas commonly involved are the middle cerebellar peduncles and the pons. However, lesions may be found everywhere, especially during the advanced phases of the disease. Spinal cord white matter can also be involved, especially in the cervical region. Marburg variant of the demyelinating disease is typically characterized by the most extensive involvement of the myelin. Demyelinating lesions are seen in T2 weighted images and in the fluid-attenuated inversion recovery (FLAIR) sequences as hyperintense foci. T1 weighted images contain hypointense foci. Enhancement of the active foci in the T1 weighted lesions is observed after the application of contrast agent (Canellas *et al.* 2007; Simon & Kleinschmidt-DeMasters 2008; Bastianello *et al.* 2004; Pichiecchio *et al.* 2009; Chong 2004; Capello & Mancardi 2004).

No consistently successful treatment for Marburg variant MS has been described (Herndon 2003). Mitoxantrone might be a suitable treatment for Marburg variant MS due to its strong anti-proliferative effects and based on certain efficacy in MS. The diagnosis of Marburg variant MS is usually severely reduced life expectancy (Turatti *et al.* 2010).

CASE REPORT

A 24-year-old woman had been monitored for epilepsy since childhood although she had not been on long-term medication since the age of eight years. During her adolescence, she underwent radio-ablation of aberrant conduction pathways for Wolf-Parkinson-White syndrome with minimal side-effects. She also followed a permanent diet for coeliac disease. She was referred to our facility in October 2009 from a local out-lying neurology department, where she had been hospitalized for gradually progressive hemi-paresis which began in early October 2009. At that time, the patient was in the 35th week of pregnancy. As part of the specialist neurological examination, she underwent an MRI scan of the brain, which revealed multifocal involvement of the paraventricular white matter near the posterior part of the left lateral ventricle, involvement of the infratentorial cerebellar region and medulla oblongata (Figure 1). Acute MS, ADEM, Marburg variant of MS, Baló concentric sclerosis, Schilder disease and vasculitis were considered in the differential diagnosis.

The patient was under the care of the Department of Obstetrics & Gynaecology and her pregnancy was ended by Caesarean section in the 35th week of gravidity. Lactation was inhibited by medocriptine. The newborn infant showed signs of immaturity, and the birth weight was 3 000 g. After the delivery, a right-sided hemi-syndrome still dominanted the clinical picture. A lumbar puncture ruled out acute neuroinfection (0.2 g/L protein, 7 oligoclonal IgG bands [OCB] in the alkaline region). The patient was treated with 5 g intravenous methylprednisolone (IVMP). The patient's condition was complicated by infection, namely pulpitis intooth #46. Despite administration of antibiotics, the infection resulted in further progression of the right-sided hemiparesis. Intravenous Immunoglobulins (IVIG) were also introduced at a dose of 5 × 25 g.

Repeated lumbar puncture revealed synthesis of two OCB in the alkaline fraction, further 0.4 g/L protein, and 4 lymphocytes/mm^3, while both PCR and ELISA borrelia assays were negative. Results of neurophysiological examinations of Visual Evoked Potential (VEP), Brainstem Auditory Evoked Potential (BAEP) and Somatosensory Evoked Potential (SEP) were within normal ranges. Rheumatological laboratory tests were negative in all parameters. Repeat MRI scan of the brain and magnetic resonance angiography (MRA) confirmed progression of the findings, in addition, several new small foci appeared supratentorially and coalescing foci were found near the left lateral ventricle (Figure 2).

After 4 weeks, the patient was started on intensified IVMP treatment at the dose 3 × 2 g/day. During

intensive rehabilitation care, the patient's condition (the right-sided hemiparesis) improved mildly, and the patient was verticalised using a walking frame and was able to walk across the room with support. The patient was re-hospitalized in our facility on December 3, 2009, after her symptoms started. The clinical findings at this time included tetraparesis, more severely expressed on the right side, bulbar symptoms, and dysarthria. MRI scan revealed further progression of focal changes with more significant findings on the left side (Figure 3). Enteral nutrition was initiated via a nasogastric probe. Serial plasma exchange (PE) treatment was also started. The patient's clinical condition deteriorated, in particular manifesting spasms of the lower extremities. Repeat examination of the cerebrospinal fluid on 8 December 2009 revealed no pleocytosis, only borderline 0.5 g/L protein, 8 lymphocytes/mm^3. Combined antibiotic treatment (Nitrofurantoin, Ciprofloxacin) was initiated according to culture tests to treat a urinary tract infection with good effect (decrease of CRP from 67.9 to 7.9 mg/L). Chest X-ray (heart and lungs) was performed with no significant pathological findings being observed. On 8th December 2009, the patient developed signs of motor dysfunction for the first time, manifesting as epileptic paroxysms which resolved after the administration of benzodiazepines and additionally with autonomic symptoms (tachycardia 120–160 /min). Electroencephalography (EEG) evaluation revealed abnormal findings of non-specific character with a focal abnormality above the left hemisphere. On 9th December 2009, the patient suffered several consecutive seizures, approx. 1–2 minutes long, predominantly on the lower extremities, which were also accompanied by tachycardia. At that time, decerebrate convulsions or generalized paroxysmal epilepsy were considered in the differential diagnosis, and the myoclonus was non-responsive to escalating therapy (gradually 3 mg clonazepam i.v., and 1 200 mg valproate i.v. were administered). The clinical condition was characterized by progression of severe spasticity of the lower extremities. The patient was referred to the Cardiopulmonary Resuscitation and Intensive Care Unit (CARICU), University Hospital in Hradec Kralove due to the grave nature of her condition. Further microbiological examination of body fluids blood, including culture tests were performed, and the patients antibiotic therapy consisting of piperacillin (2.25 g, three times per day i.v.) was administered, along with continuous valproate (1 200 mg per day i.v.) without convulsion symptoms; her Glasgow Coma Scale (GCS) level

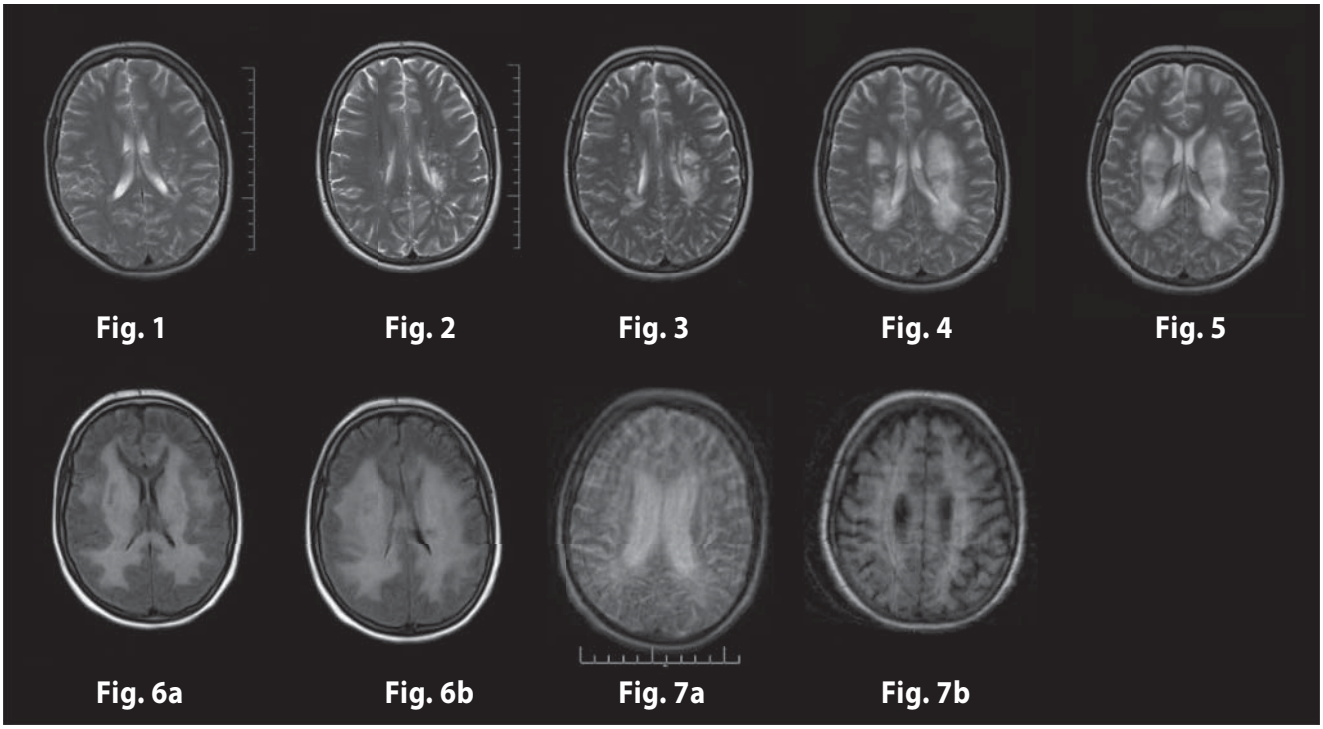

Fig. 1. Numerous paraventricular plaques around the left ventricles.
Fig. 2. Newly visible non-expanding cerebral plaques.
Fig. 3. T2 hyperintensive plaques maximally periventricularly and left paraventricularly.
Fig. 4. Progression and coalescence of the white matter plaques around the tail end of the inner capsule, the intervening basal ganglia, and coalescence of the left frontal.
Fig. 5. White matter plaques located predominantly in the centrum semiovale on the right, above the capsule and in the area of inner capsule.
Fig. 6a, b. Complete coalescence of the cerebral white matter cerebral on both sides. T2w plus further FLAIR hyperintensity maps with spared grey matter.
Fig. 7a, b. Extensive destruction of white matter, accentuated cerebral atrophy (MRI repeated 6 months from initial disease manifestation).

was 6 points. On 12th December 2009, the patient was intubated and for suspected aspiration and decrease in oxygen saturation. On 14th December, surgical tracheostomy was performed, and from15th December the patient was maintained on spontaneous ventilation, with persistent disorder of consciousness, GCS 7–8 points. During hospitalization at the CARICU, PE therapy was continued (6 series), alternatively with the administration of IVMP (in total 5 g), without any change in the patient's neurological condition. During her prolonged hospitalization at the Neurology ICU, the patient had one recurrence of Generalised Tonic-Clonic Epileptic Seizure (GTCS), while her serum valproate levels were within therapeutic range. EEG examination with low amplitude below 35 μV revealed no focal or generalized epileptiform abnormalities. Repeated MRI scan of the brain was performed and again revealed further progression of white matter involvement, which strongly suggested the progressive Marburg form of MS (Figure 4). PE therapy was discontinued (administered 6 times in total), and the patient received combined immunosuppression with cyclophosphamide (CPA) 1.0 g and IVMP 1.0 g five times every other day. Further MRI scanning revealed progressive involvement of the supratentorial white matter, now more on the right side, in the semioval center and above the capsule (Figure 5). After the administration of contrast agent, very discrete enhancement was seen in the newly progressive regions. ECG showed no abnormalities and the patient was given one pulse of mitoxantrone 20 mg IV. Percutaneous endoscopic gastrostomy (PEG) was placed to improve the quality of care. An MRI scan on 28th January 2010 revealed strong progression of the white matter involvement both supratentorially and infratentorially (T2 weighted and FLAIR hyperintense maps in the white matter with sparing of the gray matter, irregular enhancement pattern after the administration of the contrast medium suggesting a blood-brain barrier impairment (Figures 6a,b). Despite exhausting all available treatment modalities available to us (corticotherapy, IVIG, high-dose pulse immunosuppression, PE), the patient remains in poor neurological condition (comatose with tetraparesis and bulbar syndrome). Extended symptomatic palliative treatment was indicated and the patient was referred to her local catchment facility after full and frank discussion with the family. MR examination somesix months since the start of this process shows a picture dominated by extensive destruction of white matter with accented cerebral atrophy (Figures 7a,b). Clinically the patient remains in coma vigil with tetraparesis, repeated lumbar puncture shows cerebrospinal protein levels remain elevated at 0.6 g/L.

DISCUSSION

Idiopathic inflammatory-demyelinating diseases (IIDDs) include a broad spectrum of central nervous system disorders that can usually differentiated on the basis of clinical, imaging, laboratory and pathological findings. There can be considerable overlap between some of these disorders, leading to misdiagnoses or diagnostic uncertainty. Uncommon forms of IIDDs can be classified clinically into:

1. fulminating or acute IIDDs, such as the Marburg variant of MS, Baló concentric sclerosis, Schilder disease, and acute disseminated encephalomyelitis (ADEM);
2. monosymptomatic IIDDs, such as those involving the spinal cord (transverse myelitis), optic nerve or brainstem and cerebellum;
3. IIDDs with restricted topographical distribution, including Devic neuromyelitis optica, recurrent optic neuritis and relapsing transverse myelitis;
4. other forms of IIDDs are clinically and radiologically classified as pseudotumoral variants of MS (Canellas *et al.* 2007).

Fulminant demyelination disease, which is considered to be a specific form of multiple sclerosis, was first described by Marburg in 1906 in a series of three cases. This malignant form of multiple sclerosis is an extremely aggressive form of the disease, but which is fortunately very rarely encountered. It results in a significant neurological deficit or death within several weeks or months after the onset of first symptoms (Capello & Mancardi 2004). The etiopathogenesis of this variant of the disease is only partially elucidated, as with the other forms of MS. However, it is known that chemical modifications of the basic component of myelin (MBP) may cause instability of the myelin sheath (Beniac *et al.* 1999). This instability could have an importance in the pathogenesis of this specific variant of multiple sclerosis. The distribution of white matter lesions and the MRI scan recorded in our patient (especially at the beginning of the disease) are characteristic for MS. Imaging revealed large scale demyelination of the periventricular regions, white matter structures in the cerebellum, mesencephalon and medulla oblongata. The ongoing severe status of our patient is a result of massive involvement with a course lasting only several weeks. In this case, no biopsy for histopathology examination was performed, although we might expect to see a picture of extensive white matter involvement with demyelination and microbial reaction, massive infiltration of lymphocytes and macrophages, oedema from the disorder of blood-brain barrier and axonal loss as previously described in the literature (Herndon 2003; Weinshenker *et al.* 1989; Lisa & Lisy 2007; Thompson *et al.* 1997).

The differential diagnosis is very wide and includes other types IIDDs. ADEM can appear after viral disease, such as after an upper respiratory tract infection or after immunization, and can be complicated by fever. In such a case, the MRI findings can resemble MS. In

patients with ADEM, unlike the large demyelination involvement in the Marburg variant, we see instead small multiple focal lesions ocated perivascularly (Giubileu *et al.* 1997). Both ADEM and MS are caused by multifocal involvement and can both be associated with many neurological findings. Pyramidal and cerebellar symptoms as well as symptoms caused by brain stem involvement can occur in both forms. Disorders of consciousness occur more frequently in ADEM (45–75%) than in MS (13–15%) (Dale & Branson 2005; Antel *et al.* 1998) while optic neuritis is bilateral in ADEM, unlike in MS where unilateral involvement is more frequent. Epileptic seizures are reported in 13–35% cases of ADEM, while they are rare in MS (Dale & Branson 2005; Antel *et al.* 1998). Both diseases are characterized by abnormalities in the cerebrospinal fluid; the presence of intrathecal synthesis of oligoclonal IgG pattern is more common in MS patients (45–90%) than in ADEM patients (29%) (Dale & Branson 2005). In the latter, the oligoclonal pattern can disappear with time, while it is a permanent feature in patients with MS. MRI is the gold standard imaging technique for ADEM and MS. In both diseases, foci are diffusely scattered mostly in the white matter. In ADEM the margins of the lesions are not clearly demarcated and are located periventricularly in deeper structures. In contrast, in MS, the predilection site for the lesions is located in the corpus callosum and in the periaqueductal and periventricular regions (Schwarza *et al.* 2002; Kesselring 1990; Burks & Johnson 2000; Goetz 2003).

Schilder disease or Myelinioclastic Diffuse Cerebral Sclerosis is an inflammatory demyelinating disease of unknown etiology, which constitutes a distinctive clinicopathologic variant of MS affecting the white matter of brain. The disease results in one or more symmetrical, large, spherical and tumefactive demyelinating lesions in the centrum ovale and central white meter with sparing of the subcortical U fibers. The subacute onset of focal neurologic signs and increased intracranial pressure often suggests a space-occupying lesion, brain tumour or an abscess. Immunosupression with corticosteroids or with a combination of CPA induce rapid improvement in the majority of cases.

Baló disease or Encephalitis periaxialis concentrica has the characteristic pathologic findings of alternating rings of myelin preservation or remyelination and myelin loss involving regions of the cerebral hemispheres, cerebellum, brainstem, spinal cord and optic chiasma. The exact mechanism for the peculiar configuration of the plaques observed is unclear but it is likely that it represents a local phenomenom. MRI plays a central role in diagnosis of this rare disease. High doses of intravenous corticosteroids produce significant improvement of the neurologic symptoms and signs (Canellas *et al.* 2007; Simon & Kleinschmidt-DeMasters 2008). Both Baló and Schilder diseases have different pathologic demyelination findings compared to the Marburg variant and after immunosupressive treatment, partial or near complete resolution of the MRI lesions is observed along with improvement of the clinical status.

In our case, the relationship between the patient's coeliac disease status and MS is not clear. It is known that the etiopathogenesis of allergic and autoimmune diseases depend on interaction of both genetic and environmental factors, thus providing a common templatefor both these immunopathological conditions. Genetic factors also play a role in the course of an immunopathological disease, especially HLA and cytokine genes polymorphisms. Both MS and coeliac disease are associated with polymorphisms in HLA DQB1 (Bilbao *et al.* 2003; Antel *et al.* 1998). The patient in our case report had no history of immunomodulation therapy.

This case report concerns a 24-year-old woman with IIDD, Marburg variant MS or acute MS whose MRI scan showed extensive brainstem, periventricular white matter, subcortical, and cortical involvement, giving the appearance of an „MS cerebritis." The patient did not respond to treatment with methylprednisolone, and showed no improvement after immunosuppresive treatment with CPA and mitoxantrone (MiTX).

REFERENCES

1 Antel J, Birnbaum G, Hartung HP (1998) Clinical Neuroimunology. Blackwell Science, Malden, U.S. 423 pgs..
2 Bastianello S, Pichiecchio A, Spadaro M, Bergamaschi R, Bramanti P, Colonnese C, Sabatini U, Uggetti C, Luccichenti G (2004) Atypical multiple sclerosis: MRI findings and differential diagnosis. Neurol Sci. **25 Suppl 4:** S356–60.
3 Beniac D, Wood D, Palaniayar N, Ottensmeyer P, Moscarello M, Harauz G (1999) Marburg's variant of multiple sclerosis correlates with less Compaq structure of myelin basic protein. Mol Cell Biol Res Commun. **1:** 48–51.
4 Bilbao JR, Martín-Pagola A, Pérez De Nanclares G, Calvo B, Vitoria JC, Vázquez F, Castańo L (2003) HLA-DRB1 and autoimmunity: common associated alleles in autoimmune disorders, Ann N Y Accad Sci. **1005:** 314–318.
5 Blumhardt LD (2004) Dictionary of Multiple Sclerosis. Martin Dunitz Ltd London. United Kingdom, 182 pgs.
6 Burks JS, Johnson KP (2000) Multiple sclerosis – Diagnosis, Medical Management and Rehabilitation. Demos Medical Publishing. New York. U.S. 598 pgs.
7 Canellas AR, Gols AR, Izquierdo JR, Subirana MT, Gairin XM (2007) Idiopathic inflammatory-demyelinating disease of the central nervous system. Neuroradiology. **49(5):** 393–409.
8 Capello E, Mancardi GL (2004) Marburg type and Baló's concentric sclerosis: rare and acute variants of multiple sclerosis. Neurol Sci. **25 Suppl 4:** S361–363.
9 Chong HT, Ramli N, Lee KH, Kim BJ, Ursekar M, Dayananda K, Singhal BS, Chong J, ChanLL, Seetoh YY, Chawalparit O, Prayoonwiwat N, Chang FC, Tsai CP, Tang KW, Li PCK, Tan CT (2004) Magnetic resonance imaging of Asians with multiple sclerosis was similar to that of the West. Neurology Asia. **9:** 47–53.
10 Dale RC, Branson JA (2005) Acute disseminated encephalomyelitis or multiple sclerosis: can the initial presentation help in establishing a correct diagnosis? Arch Dis Child. **90:** 636–639.
11 De Seze J (2006) Bordelines types of multiple sclerosis. Rev Neurol Paris. **162(1)**: 137–143.
12 Giubileu F., Sarrantonio A., Tisei P., Gasperini C., Salvetti M. (1997) Four-year follow-up of a case of acute multiple sclerosis of the Marburg type, Ital. J. Neurol Sci. **18:** 163–166.

13 Goetz CG (2003) Textboock of Clinical Neurology, Saunders, Philadelphia,U.S. p. 1059–1082.
14 Havrdová E *et al.* (2001) Neuroimunologie. Prague: Maxdorf Czech Republic. p. 142–179.
15 Herndon RM (2003) The pathology of multiple sclerosis and its variant. In: Multiple sclerosis: immunology, pathology and pathophysiology. Demos Medical Publishing. New York. U.S. p. 185–197.
16 Johnson MD, Lavin P, Whetsell WO (1990) Fulminant monophasic multiple sclerosis, Marburg´s type. J Neurol Neurosurg Psychiatry. **53**: 918–921.
17 Kesselring J, Miller DH, Robb SA, Kendall BE, Moseley IF, Kingsley D, du Boulay EP, McDonald WI (1990) Acute disseminated encephalomyelitis. MRI findings and the distinction from multiple sclerosis. Brain. **113:**291–302.
18 Lisá I, Lisý L (2007) Akútne leukoencefalopatie. [(Acute leukoencephalopathy.)(In Czech:Neurol. pro praxi.)] **2:** 94–98.
19 Pichiecchio A, Tavazzi E, Maccabelli G, Precupanu CM, Romani A, Roccatagliata L, Luccichenti G, Bergamaschi R, Bastianello S (2009) What insights have new imaging techniques given into aggressive forms of MS--different forms of MS or different from MS? Mult Scler. **15(3):** 285–93.
20 Schwarza U, Marino S, Hess K (2002) Marburg's Encephalitis in a Young Woman. Eur Neurol.l **48:** 42–44.
21 Simon JH, Kleinschmidt-DeMasters BK (2008) Variants of multiple sclerosis. Neuroimaging Clin N Am. **18(4):** 703–716.
22 Thompson AJ, Polman C, Hohlfield R (1997) Multiple sclerosis – Clinical Challenger and Contraversies. United Kingdom London: Martin Dunitz Ltd. 360 pgs.
23 Turatti M, Gajofatto A, Rossi F, Vedovello M, Benedetti MD (2010) Long survival and clinical stability in Marburg´s variant multiple sclerosis. Neurol Sci. **31 (6):** 807–811.
24 Weinshenker BG, Bass B, Rice GPA et al (1989) The Natural history of multiple sclerosis: a geographically based study. In: Clinical course and disability. Brain. **112:** 133–146.