A Case of Marburg's Variant of Multiple Sclerosis Successfully Treated with IVIg and Mitoxantrone

Introduction

Marburg's variant of multiple sclerosis is a malignant form of MS that evolves rapidly leading to death or severe disability. Otto Marburg first described this severe form of MS in 1906, where he described 3 cases of severe form of multiple sclerosis with large central nervous system lesions.[1] Since then the disease was called as Marburg's variant of MS. Patients usually present with focal neurological deficits or seizures. They often show acute neurological deterioration and succumbs to death in few weeks to months due to brainstem involvement.[2,3] We present a case report of an older adult female who presented with Marburg's variant of multiple sclerosis.

Case Report

A 55-year-old female patient presented with one episode of generalized tonic clonic seizure. Postictally she remained in altered sensorium. At the time initial presentation her GCS was 7/15 with right sided hemiparesis. She was intubated due to low GCS and kept on ventilator support. She had been under treatment for major depressive disorder for the past 5 years.

Patient underwent magnetic resonance imaging (MRI) of brain which showed a large ill-defined lesion in the left frontal lobe involving the centrum semiovale and ganglio capsular region [Figure 1]. It was crossing the midline involving the cingulate gyrus, genu, body, and splenium of the corpus callosum with brain stem involvement. It displayed iso to hypointense in T1WI and predominantly hypreintense signal in T2WI. Postcontrast study showed patchy internal and thin rim of incomplete peripheral enhancement. There were gyral swellings with no midline shift. MR spectroscopy showed elevated choline peak in most of the regions with reduction in the NAA and tall lactate peak. MRI spine screening was normal. Repeat MRI was done after 3 days and it showed extensive progression of the lesions involving bilateral basal ganglia, brainstem till the medullary level and bilateral cerebellar peduncles.

Cerebrospinal fluid (CSF) analysis was done which showed normal sugar and cell count, but slight increase in protein level (68 mg/dl). Oligoclonal bands were absent. CSF culture and vasculitis work ups were negative. She was also tested for antiMOG and antiaquaporin-4 antibodies, which turned out to be negative.

On the basis of the acute onset and rapid progression of the disease, clinical, radiological, and biochemical analysis a diagnosis of acute fulminant demyelinating disorder Marburg's variant of MS was made. Patient was started on high dose methyl prednisolone at a dose of 1000 mg/day. In view of unresponsiveness to corticosteroid treatment intravenous immunoglobulin (IVIg) was initiated along with single dose of Mitoxantrone 12 mg. Post-IVIg treatment she was started on azathioprine. Azathioprine was stopped after 7 days due to leucopenia. She was tracheostomized as she needed long-term ventilator support. Gradually she showed signs of improvement and was weaned off from ventilator in around 4 weeks. At the time of discharge her GCS was E4VtM6 with right hemiparesis 3/5. MRI brain was done after 3 weeks, which showed significant reduction in size of lesions. She showed a stable improvement over a period of months and has completed 2 years of relapse free survival.

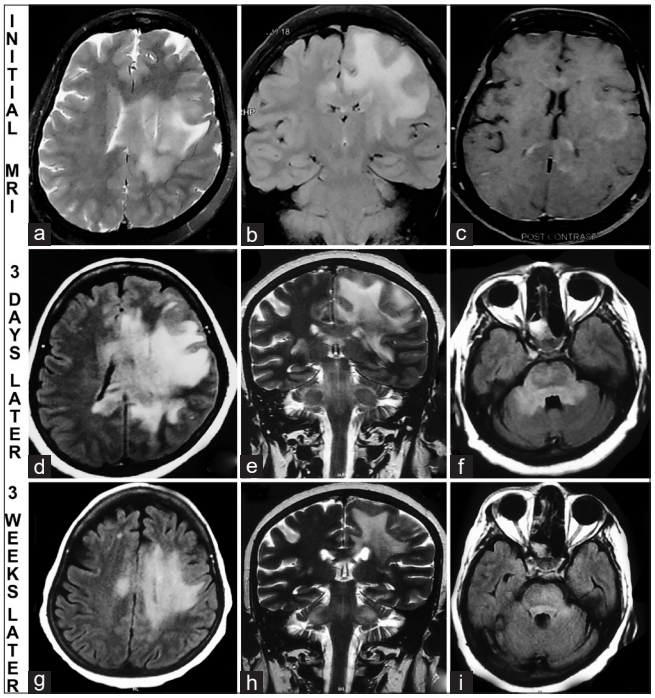

Figure 1: MRI Brain on initial presentation - (a) T2WI axial, (b) T2 FLAIR coronal sections show hyperintense lesion involving the centrum semiovale, corpus callosum, deep cerebral nuclei and corpus callosum. (c) T1WI contrast axial section shows ill-defined enhancement within the lesion. MRI brain after 3 days - (d) T2WI axial, (e) T2 FLAIR coronal, (f) T2 FLAIR axial sections show increase in size of the lesion with bilateral involvement and extension into brainstem. Repeat MRI after 3 weeks - (g) T2 FLAIR, (h) T2WI coronal, (i) T2 FLAIR axial sections show regression of the lesion

Discussion

Rapidly evolving severe forms of multiple sclerosis like Marburg's variant and Balo's concentric sclerosis account for less than 4% of total incidence of MS. The clinical course is rapid and often fatal. The exact etiology behind this

malignant nature of Marburg's variant MS is unknown. This aggressive course can be due to involvement of vital areas like brainstem or due to an unusual aggressive immunological or pathological process.[4] In our case the repeat MRI showed extensive involvement of the brainstem. It has been reported that the myelin basic protein (MBP) isoform seen in Marburg's variant is a larger one weighing 18.5 kDa, which is less cationic than the normal MBP or MBP isoforms seen in other MS cases.[5,6] The increase in molecular weight and reduced cationic property is due to the deimination of arginyl residues to citrulline.[2] This biochemical change causes structural instability of the central myelin sheath and this contributes in the pathogenesis of Marburg's variant MS.[7]

The clinical presentation is often acute with neurological deficits like decreased mental status, hemiplegia, aphasia, seizures, etc., depending upon the structures involved.[4] Symptoms evolve rapidly than in the common forms of MS.

Demyelinating plaques are seen in supratentorial as well as subtentorial areas like brainstem, such as the lower brainstem, but more frequently there is the presence of large tumour-like demyelinating plaques in the centrum ovale.[4] Brain and spinal cord MRI shows large T2-weighted (T2WI) hyperintense lesions disseminated throughout the hemispheric white matter and brain stem, often with mass effect and edema. The lesions may show enhancement ongadolinium. MR spectroscopy shows increase of the peak of choline and a decrease of *N*-acetyl-aspartate (NAA) as seen in other demyelinating conditions.[4]

CSF examination shows increase in proteins with no or minimal increase in cellularity. As in other forms of MS, oligoclonal bands may also be present but less often.[4]

Neuropathological examinations mostly reveal that all the plaques are of recent origin with extensive demyelination, although old plaques have occasionally also been described.[4] Other neuropathological features seen are significantly reduced or absent oligodendrocytes, relative preservation of axons, extensive cellular infiltration by giant astrocytes, macrophages and microglia, and reactive astrocytosis.[4,8,9]

Differential diagnosis includes multifocal brain tumours, infectious, metabolic, vascular, and demyelinating disorders, such as Balo's concentric sclerosis, Schilder's diffuse sclerosis, and acute demyelinating encephalomyelitis (ADEM).

Balo's concentric sclerosis has a typical histological feature of alternating layers of myelin loss and myelin preservation or remyelination. This is seen as concentric rings in T2WI and T1WI contrast MRI.[4,8] Schilder's diffuse sclerosis is a very rare disease seen in children and MRI shows one or two large lesions, often bilateral involving the centrum semiovale with no significant peripheral edema.[10] The MRI appearance in our patient was different from these characteristic features.

ADEM is another fulminant demyelinating disease which progress over days and attains rapid remission. It occurs due to an autoimmune response to the MBP following an infection or immunization, predominantly occurs in younger age groups. ADEM lesions extends into grey matter unlike other forms of MS.[11] ADEM has a stable disease process compared to other fulminant MS and serial MRI shows absence of any new lesions.[12] In our case, patient was an older adult with no history of any infection or vaccination and more importantly serial MRI showed new lesions.

Our patient had no history or signs of an infectious, metabolic, or vascular pathology. Hence, a diagnosis of Marburg's variant of MS was made by exclusion. A detailed clinical history, neurological evaluation, CSF analysis, and serial MRI together leads to a correct diagnosis of this disease.

The first line treatment is a course of intravenous steroids but often the disease is unresponsive to high dose steroids. IVIg can be considered in cases not responding to steroids. Our case was not showing adequate improvement on steroid therapy and a course of IVIg was given which was found to be effective. Cycles of plasmapheres is also has shown positive results in unresponsive cases.[13]Mitoxantrone is a potent anthracenedione with both immunosuppressant and immunomodulatory properties with proven efficacy in worsening relapsing-remitting (RR) and secondary progressive MS.[14] Some patients with Marburg's MS treated with mitoxantrone has shown improvement.[3] We had given single dose of mitoxantrone but the individual efficacy of the drug in arresting the disease progression cannot be assessed in our case as we had combined other medications. Another study has shown improvement with high dose cyclophosphamide in failed first line treatment.[15] In patients with no signs of improvement with steroid therapy, IVIg, plasmapheresis or conventional immunosuppressants an intense immunosuppression followed by autologous stem cell transplantation can be considered.[4]

Conclusion

Marburg's variant of MS has an acute, quickly progressive malignant course unlike the typical MS which is more of a chronic disease. Our patient recovered from a very critical status and currently in her third year of remission despite residual disabilities. This finding suggests that some patients respond well to appropriate treatment and shows a longer period of remission unlike most of the patients having fatal clinical course.

Declaration of patient consent

The authors certify that they have obtained all appropriate patient consent forms. In the form the patient(s) has/have given his/her/their consent for his/her/their images and other clinical information to be reported in the journal. The patients understand that their names and initials will not be published and due efforts will be made to conceal their identity, but anonymity cannot be guaranteed.

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Conflicts of interest

There are no conflicts of interest.

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