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Marburg variant of multiple sclerosis; a diagnostic and therapeutic challenge

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MARBURG VARIANT OF MULTIPLE SCLEROSIS; A DIAGNOSTIC AND THERAPEUTIC CHALLENGE

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ABSTRACT

Marburg variant of multiple sclerosis (MS) is a highly aggressive, fulminant demyelinating disease with very high morbidity and mortality. Early diagnosis and aggressive management is vital to limit severe disability and improve the outcome. We present a case of 35 years old male who presented with rapidly progressive demyelinating illness, leading to bed bound status over the course of a month. He was treated aggressively with intravenous (IV) steroids, plasma exchange (PLEX) and Mitoxantrone (MTX), leading to a remarkable recovery.

Key words: Multiple sclerosis, demyelinating, fulminant.

INTRODUCTION

Marburg variant of MS or Fulminant multiple sclerosis (FMS) is a rare but highly aggressive disease. It is characterized by rapidly progressive deterioration of neurological symptoms, sometimes, even weeks or months after the first attack [1]. This results in progressive widespread white matter destruction in cerebral cortex but may even extend to involve vital brainstem structures [2,3]. Management of FMS is very challenging as the outcome in many cases is either severe disability or death. Treatment options for FMS include high dose corticosteroids, serial plasma exchange transfusions, immunoglobulins and disease modifying agents (Mitoxantrone and Cyclophosphamide) [4,5,6,7,8,9]. Patients also need intense involvement of various support services to help them during periods of disability. We present a case of acute FMS who showed relatively rapid and effective recovery when treated early and aggressively.

CASE REPORT

A 35 years, otherwise healthy gentleman was seen in our neurology clinic for sudden onset left hemiparesis, dysarthria, diplopia and blurring of vision lasting a few days followed by partial recovery. There was no history of fever or antecedent infection. He underwent cranial MR imaging which revealed multiple nodular lesions, isointense on T1 and hyperintense on FLAIR and T2 weighted images suggesting a demyelinating disorder or metastatic disease (Fig.1). He was prescribed IV methylprednisolone 1gm once daily for 5 days. He did not start treatment immediately and took 2 doses only. 10 days later, he presented to emergency department with new onset right hemiparesis, right UMN facial palsy, motor aphasia and acute confusional state. Repeat MR imaging showed interval increase in size of previously noted lesions plus new lesions suggestive of fulminant multiple sclerosis vs ADEM (Fig.2). He was severely disabled (EDSS 9) and was admitted to intensive care unit for aggressive therapy. CSF examination and Visual evoked potentials were also obtained (Table 1). He was given remaining 3 doses of IV methylprednisolone (1000 mg) and was started on PLEX (250ml/kg divided over 7 sessions; day 1,2,3,5,7,9,11).

Table 1. Pertinent Investigations

Investigations	Results		
ESR	1 mm/hour	n=582	
CBC	TLC : 10,000/µl	Hb : 16.70 g/dl	Platelets : 211,000/µl
CRP	4.66 mg/L		
PSA	0.728 ng/mL		
Creatinine	0.76 mg/dL		
CSF analysis	WBCs: <5 cells/µL,	Protein: 81.3mg/dL	OG bands: positive
ACE levels	<5.0 U/L		
LFTs	T. Bilirubin: 0.7mg/dL, ALT: 24, Alk. Phosphatase: 30U/L		
Chem 7 (mEq/L)	Sodium: 133, Potassium: 3.9, Chloride: 99, Bicarbonate: 21		
VEP (visual evoked potentials)	P100 values: Right: 125.4 ms, Left: 130.8 ms		
Vitreous examination	No immune complexes seen in vitreous		
CT chest, abdomen, and pelvis	Negative for malignancy /infection		

Aggressive speech therapy and physiotherapy were also done. Metastatic workup was ordered with CT chest, abdomen and pelvis as were other investigations that

came to be negative for malignancy. ANA was not done. Patient showed gradual improvement in his clinical status and was discharged home 12 days later. He was given IV Mitoxantrone (12mg/m2), first dose given on 12 day post admission and then once every 3 months.

Table 2. Differences between MS and ADEM

Characteristics	ADEM	MS
Age	<8 years	≥8-10 years
Antecedent infection	usual	unusual
Encephalopathy	Common	Uncommon
CSF pleocytosis	Prominent	Uncommon
Oligoclonal bands	Absent	Present
MR imaging (gray matter involvement	Common	Uncommon
Course	Monophasic, Non-progressive	Multiphasic, progressive, Relapsing & remitting
Disease modifying therapy	Not required	Required to prevent relapses

On discharge, EDSS improved from 9 to 5. He was followed in neurology clinic 3 months later with repeat MR imaging which showed interval regression in the size of previously noted lesions with no new activity (Fig.3). He showed remarkable clinical improvement, walking without support (EDSS 2) (Fig.4). He had no further relapse at 3 months.

DISCUSSION

Multiple sclerosis is the most common, idiopathic, inflammatory demyelinating disease of central nervous system with a relapsing and remitting course [1] Approximately 7% of patients may present with a fulminant disease [10]. Tumefactive multiple sclerosis refers to large demyelinating lesions, typically 2 cm or larger in size, with surrounding mass effect, perilesional edema and open ring enhancement on gadolinium contrast [11,12,13].

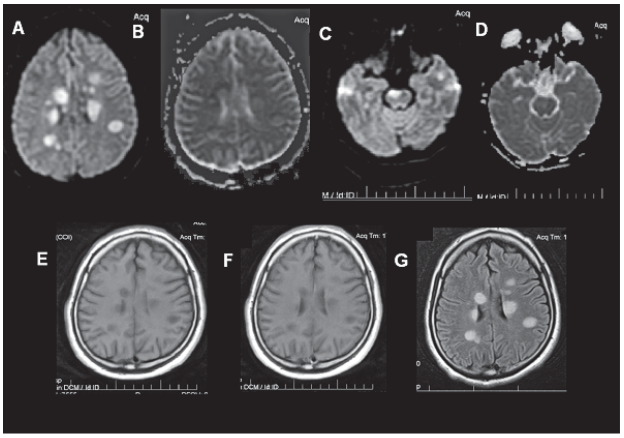


Figure 1. Axial diffusion weighted images(DWI) of Brain (A) and (C) showing multiple nodular lesions of diffusion restriction in bilateral parietal periventricular and subcortical regions, corresponding ADC images (B) and pons (D), largest one measuring 2.7×1.4 cm2. They are iso-intense/hypointense on T1 (E) with subtle peripheral contrast enhancement (F) and correspondingly bright on FLAIR image with surrounding halo (G) and no significant mass effect.

First described nearly a century ago, Marburg variant of MS is a rare, acute, monophasic and highly aggressive form of MS, leading to severe morbidity or mortality within a few weeks to months.[1] Due to its atypical clinical and radiographic features, it poses significant diagnostic dilemma [14]. It presents with a polysymptomatic, monophasic illness [15] suggesting diffuse and extensive CNS involvement.

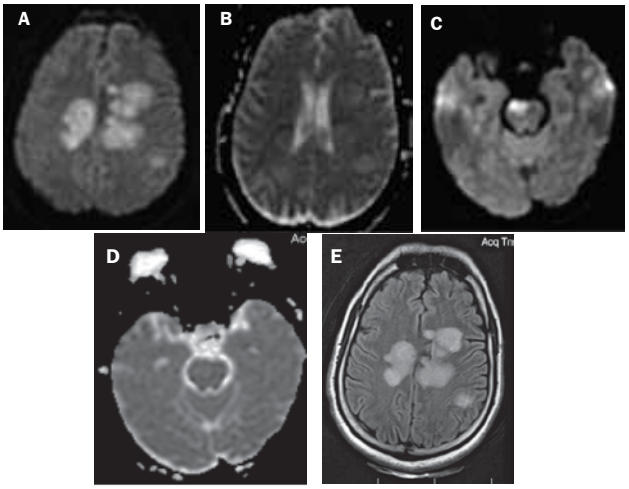
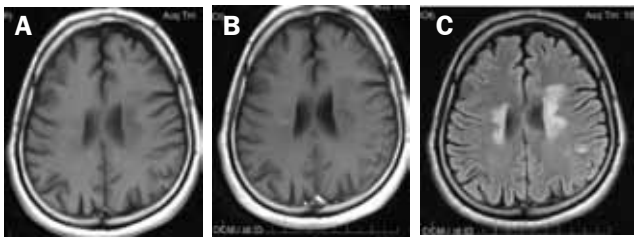


Figure 2. Follow up MR images obtained 10 days later with new onset right hemiparesis and acute confusional state. DWI (A and C), ADC (B and D)and axial FLAIR images(E) showing development of new lesions and interval increase in size of previously observed multiple lesions which have become more confluent bilaterally.

Unlike classical MS, lesions occur simultaneously in all affected areas with large zones of confluent demyelination,[1,16] including cerebral hemisp- heres and brainstem [17] High mortality is associated with this variant especially with involvement of brainstem structures, [12,18,19] necessitating intensive care for aggressive management [15].First presentation of an acute, fulminant demyelinating event is the most common presentation in the course of tumefactive MS,13 hence early and prompt recognition of disease process and exclusion of infective, neoplastic, vasculitic and granulomatous disorder is of paramount importance.

Figure 3. Follow up MR images of same patient obtained at 3 months after resolution of acute neurological dysfunction. Axial T1 pre (A), post contrast (B) and FLAIR (C) images showing regression in size of previously noted lesions with no abnormal post contrast enhancement.



As our patient had no previous history of MS, it was difficult to differentiate it from other varieties of malignant demyelinating diseases especially ADEM. However, historical data, CSF analysis and radiographic characteristics of lesions suggested fulminant MS (table 2) [20]. Radiological images were almost diagnostic of tumefactive demyelinating process based on size (2cm or more), location (periventricular and juxtacortical) and nature of lesions (confluent areas, mixed T2 weighted iso and hyperintensity of enhanced regions, absence of cortical involvement and absence of a mass effect) [14,15,21,22] The lesions can be multifocal (83%) (as in our case) or unifocal (17%)[13] CSF analysis in our patient revealed absence of pleocytosis with elevated protein and presence of oligoclonal bands which is present in 11% to 33% of tumefactive MS cases,[13] favouring our diagnosis of tumefactive MS over ADEM. [23] Biopsy of the lesions is not routinely recommended to make a histological diagnosis. Standard treatment approach for fulminant MS variants is similar to severe relapses of MS. However, due to the rarity and high mortality associated with Marburg variant of MS, only a limited number of case reports have shown some promising results for Plasma exchange and Mitoxantrone as treatment for acute phase and prevention of further relapses [4,5,24] There is one published study of Fulminant MS from Pakistan also from our centre where patients were treated with IV immunoglobulins followed by Mitoxantrone, with good outcomes[22].

Fig 4. Follow up of patient in neurology clinic 3 months later.

We used Plasma exchange (PLEX) in this patient due to financial constraints. Mitoxantrone is an immunomodulatory agent used as a disease modifying drug (DMD) to improve neurological disability and delay progression in relapsing remitting MS and secondary progressive MS [21]. Several randomized clinical trials used 12mg/m2 dose administered once every 3 months [21]. We have previously used mitoxantrone for management of relapsing remitting MS [23] and as a DMD for Fulminant MS.22 Though FMS is a disease of severe morbidity and high mortality but better outcome can be expected if treated promptly and aggressively with disease modifying therapies early in the course of the disease.

CONCLUSION

Due to limitation of resources in our country, PLEX followed by Mitoxantrone may be a valuable option for treatment of fulminant multiple sclerosis.

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Sadia Imtiaz: Study concept and design, data collection, data analysis, manuscript writing, manuscript review

Maimoona Siddiqi: Study concept and design, data collection, data analysis, manuscript review

Arsalan Ahmed: Data collection, data analysis, manuscript writing, manuscript review