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Original article

Multiple sclerosis lesions on magnetic resonance imaging, their characterization and pathological correlation with musculoskeletal disability in Pakistanis

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Background: Multiple sclerosis (MS) is an inflammatory disease affecting movement. MS has a worldwide distribution.
Objectives: Early detection of MS lesions in Pakistanis by magnetic resonance imaging (MRI); to describe characteristics and to determine the association with musculoskeletal disability.
Methods: We included 100 patients (18–65 years old) diagnosed with cases of MS from March 2012 to March 2013. A detailed clinical history of the musculoskeletal system was taken and MR imaging was performed to characterize lesions acquiring T1-weighted (T1W), T2W, proton density, fluid-attenuated inversion recovery (FLAIR), and T1W postgadolinium sequences.
Results: Most patients belonged to a middle-aged group (42–62 years) and MS was common in women. MS lesions were found in the deep white matter of central nervous system (95 patients), supratentorially (97), periventricularly (96), juxtacortically (62), infratentorially (16), and in the temporal lobes (9). T2W sequences (99 patients detected) were superior to T1W sequences (47). By contrast, FLAIR sequence was more accurate and 100% of these cases were detected on this sequence of MRI. Muscle spasticity was found in 10 patients, muscle weakness in 53, uncoordinated movements in 7, ataxic gait in 9, and slurred speech in 3. However, numbness remained the more common clinical history (69 patients). Muscle fatigue (19), hemiparesis (8), and monoparesis in either upper and lower limbs (5) were other clinical presentations.
Conclusions: MRI plays a pivotal role in detection and characterization of MS plaques. Clinical manifestations and imaging findings are similar to those reported from other parts of the world.

Keywords: Ataxia, FLAIR, MRI, multiple sclerosis, muscle weakness, spasticity, T1W1, T2WI

Multiple Sclerosis (MS) is also known as encephalomyelitis disseminates or disseminated sclerosis [1]. MS is characterized by relapses and remission and is an autoimmune cell mediated demyelinating disease of the CNS. It is the commonest cause of neurological deficit in young adults. Disease onset usually occurs in adolescence and is more common in women. Jean-Martin Charcot first described MS in 1868 [2]. The estimated global prevalence of MS is 3 per million. Its prevalence is greatest in Europe (8 per million), followed by the Eastern Mediterranean (1.4), America (0.83), Western Pacific (0.5), Southeast Asia (0.28), and Africa (0.03) [3].

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The brain areas predominantly involved in MS include the periventricular or juxtacortical white matter, basal ganglia, optic nerves, cerebellum, brainstem, and spinal cord. The white matter carries signals between grey matter areas, which after processing reaches the body [4]. Previously MS was considered as a white matter inflammatory-demyelinating disease and is still classified as a disease of the white matter. The most important pathological processes in white matter lesions are inflammation and demyelination, with neurodegeneration being a late process. However, recent studies from pathological and quantitative magnetic resonance imaging (MRI) suggests that neither of these concepts holds true [5]. MS is a more global disease of the CNS. The white matter tissue plaques can appear grossly normal. Neurodegeneration may start earlier in the course of disease. The relationship between inflammation and demyelination, and neurodegeneration remains

unclear. However, recent studies suggest that neurodegeneration is the cause behind irreversible damage in MS and it involves both white and gray matter, where it may be an important factor in long-term disability [6].

MS can present as any sort of sensory and motor deficit including changes in motor and sensory sensations, such as tingling or loss of sensitivity, numbness or pricking (hypoesthesia and paresthesia), spasms and muscle weakness, difficulty in moving or clonus; problems in speech (dysarthria) or swallowing (dysphagia), difficulties with coordination and balance; optic neuritis including diplopia and nystagmus, fatigue, acute or chronic pain, and bowel and bladder difficulties [7].

The diagnosis of MS was revolutionized by introduction of MRI in 1981, which can describe the substantial disease activity in brain even in absence of overt clinical features [8]. MRI is the most important diagnostic tool in neuroimaging of the brain and spine, such as T2-weighted (T2W), diffusion weighted, gadolinium MRI contrast agent, and magnetic resonance spectroscopy (MRS) that shows areas of hyperintense signals (lesions or plaques) suggesting demyelination. MRS also provides information about the brain biochemistry. Prognosis of MS depends on its early diagnostic capability, age, sex, its initial symptoms, degree of disability, and the cognitive disturbances [9].

MRI principles are based upon the magnetism of the nucleus of hydrogen atoms having one proton present in water or lipids. The time taken for the transversal magnetization vector to return to its original resting longitudinal magnetization vector is called T1 relaxation time. The time for immediate decay of transversal magnetization after withdrawal of a radiofrequency pulse is called T2 relaxation time. Fat has relaxation time of 250 ms on T1 and 80 ms on T2. Liver has relaxation time of 400 ms on T1 and 40 ms on T2. White matter has relaxation time of 650 ms on T1 and 90 ms on T2. Mostly spin-echo sequences are used; TR (repetition time) is the time elapsed between the start of the first 90° radiofrequency pulse and the start of consecutive 90° radiofrequency pulse. TE is the time lapsed from the start of pulse until the production of echoes. By changing TR and TE we can make differently weighted images such as T1W images. TR = 1000 ms and TE = 30 ms, T2W images. TR 3000 and TE ≤ 100, proton density images use the TR of T2W and TE of T1W images. MS plaques on T1W are hypointense, and on T2W are hyperintense [8]. The usual techniques performed for MS are T1W, T2W, and FLAIR. The FLAIR images also show the lesions as hyperintense. In some 50–70 patients, the MS lesions are clinically silent despite that a patient may have optic neuritis, a brainstem syndrome and spinal cord syndrome, but these lesions can be disclosed by T2W images [10] and their presence indicates a higher likelihood of developing clinically definite MS. To diagnose MS, there have been different criteria. More recently, the McDonald Criteria [11], which were later on revised in 2005 [12], and again in 2010, and published in 2011 [13] have been developed for better and more reliably diagnosis of MS.

These criteria include the MRI features in the established diagnostic workup and clinical history and lab examination. But, while these T2 lesions predict conversion to clinically definite MS [14], they only predict subsequent disability to a limited degree [10]. Whilst pathological studies have confirmed that these T2 lesions correspond with the MS plaques, these lesions lack pathological specificity being driven by inflammation, demyelination, edema, and axonal loss and remyelination [15]. White matter T2W lesion load has frequently been included in treatment trials to assess the response to the disease modifying treatment and assess disease progression [16]. While the presence of demyelinating lesions in the cortex has been long known, their significance has been largely ignored [17]. This is because, at least in part, in conventional MRI most of lesions in the gray matter are not visible and despite improved sequences they remain largely undetected. Certainly, other factors such as poor visualization of these lesions with the conventional histological staining methods have played a role on disregarding these lesions [18].

Gadolinium (Gd), a paramagnetic element, (which has seven unpaired electrons in its electronic structure) when chelated to, for example, diethylene-triamine-pentaacetic acid (DTPA; one of a number of chelators currently used) to eliminate the toxic effects of free Gd, is used as contrast agent in MRI. Chelated Gd is given intravenously; despite being too large a molecule to cross the blood-brain barrier quickly, it can slowly leak into brain tissues, but rapidly accumulates in lesions where the blood–brain barrier is disrupted resulting in "enhancement" of active MS lesions. Gd-enhanced lesions are used in MS treatment trials to monitor the disease activity. Gd enhancement has been associated with histopathological evidence of active inflammation

and demyelination [19] and is a consistent feature of new lesions (lasting typically for several weeks) in relapsing forms of MS.

To our knowledge, a study of musculoskeletal system disabilities of MS patients has not yet been conducted in Pakistan. Our aim was to improve health awareness for early detection and diagnosis of MS with the help of diagnostic techniques such as MRI. As clinical presentation, severity of the disease, and other epidemiological variables vary from individual to individual and also population to population. Musculoskeletal disability manifestations from numbness at one end of the spectrum of disease to the other extreme of paresis can be presenting feature of MS. We aimed to report in the present study, the association of various disabilities of musculoskeletal system with Pakistani patients with MS.

Materials and methods

The study protocol was approved by the research committee and Institutional Review Board of King Edward Medical University (approval No. 249/RC/KEMU). All patients suspected with MS, aged 18–65 years who came to the Radiology and Neurology Departments, Mayo Hospital, King Edward Medical University (KEMU), Lahore, and Institute of the Punjab, where MRI facilities are available were screened for the present study. After IRB approval, we enrolled 100 patients fulfilling the inclusion criteria, with cases of MS diagnosed from March 2012 to March 2013, in the present study. Informed written consent was obtained from participants before they were included. Patients with a history of alcohol or drug dependence, major psychiatric illness, neurological disease other than MS, and gross visual impairment were excluded. A detailed clinical history regarding musculoskeletal system was taken and imaging was performed on an MRI system (Philips Intera/Achieva 1.5 T Nova Dual) acquiring T1W, T2W, proton density, FLAIR, and T1W postgadolinium sequences. Lesion characterization was performed by MRI using T1W, T2W, and postcontrast T1W scans, and FLAIR. Lesions were T1-hypointense, T2-hyperintense, and showed incomplete ring enhancement on postcontrast scanning (more specific for MS) and explained by McDonald's criteria. Cortical lesion detection, typing, and image interpretation was performed by a neuroradiologist with clinical and imaging experience in MS. All the data was collected in preformed proforma and data was entered into SPSS Statistics for Windows, version 17 (SPSS Inc, Chicago, IL, USA) and was analyzed using the same software.

Results

In the present study, patients were 18 to 65 years old with mean age of 43.1 (SD 13.88) years. Most patients with MS were 42 to 62 years old group (47%), while 30% cases were found those 18 to 38 years old, and rest (23%) were >62 years. There were 43 male and 57 female patients. Considering MS lesion involvement of the brain parenchyma, MS lesions mainly involved deep white matter of the CNS. Deep white matter lesions were present in 95% of the cases. MS plaques were present in temporal lobe, but in small number of cases (**Table 1**). The lesions were more common supratentorially, but can be present in infratentorial locations, including the posterior fossa and spinal cord as found in 16% of our cases (**Table 1**).

Table 1. Frequency of lesions in patients with multiple sclerosis

Symptoms	No. of patients
Deep white matter disease	95
Temporal lobe lesions	9
Juxtacortical lesions	62
Periventricular lesions	96
Infratentorial lesions	16
Supratentorial lesions	97

On clinical history, musculoskeletal symptoms included muscle spasticity, muscle weakness, uncoordinated movements and ataxic gait, and slurred speech. Numbness was the more common clinical history (**Table 2**). Muscle fatigue was a common clinical presentation in younger patients (<39 years). Psychosomatic effects, e.g. sensory or motor system problems were found in 70 patients with MS detected on MRI. We found 54 cases with musculoskeletal problems, e.g. hemiparesis or monoparesis (**Table 2**), 2 cases had genitourinary symptoms.

No specific relationship between prevalence of MS with socioeconomic status (**Table 3**) was found, but a familial trend was suggested in 20% of cases.

T2W sequences were more sensitive than T1W sequences for detecting MS lesions on MRI. T2W imaging sequences identified 99% patients with MS lesions (**Figure 1**; **Table 4**) compared with 47% on

T1WI (**Figure 1**; **Table 4**). By contrast, FLAIR sequences were the most accurate, and 100% of the present cases of MS were detected using this (**Figure 1**; **Table 4**).

The mean number of lesions in each brain area is reported in **Table 5**.

Table 2. Pathological correlation of multiple sclerosis with musculoskeletal disability

Symptoms	No. of patients
Musculoskeletal disease	54
Psychosomatic effect	70
Fatigue disease	19
Blurred vision	48
D. Pallor	25
Numbness	69
Slurring speech	3
Ataxic gait	9
incoordination	7
Spasticity	10
Weakness	53
Eye/vision problems	57

Table 3. Distribution of patients according to occupation

Name	Patients
Govt. servant	21
Businessman	18
Shopkeeper	9
Teacher	15
Others	37
Total	100

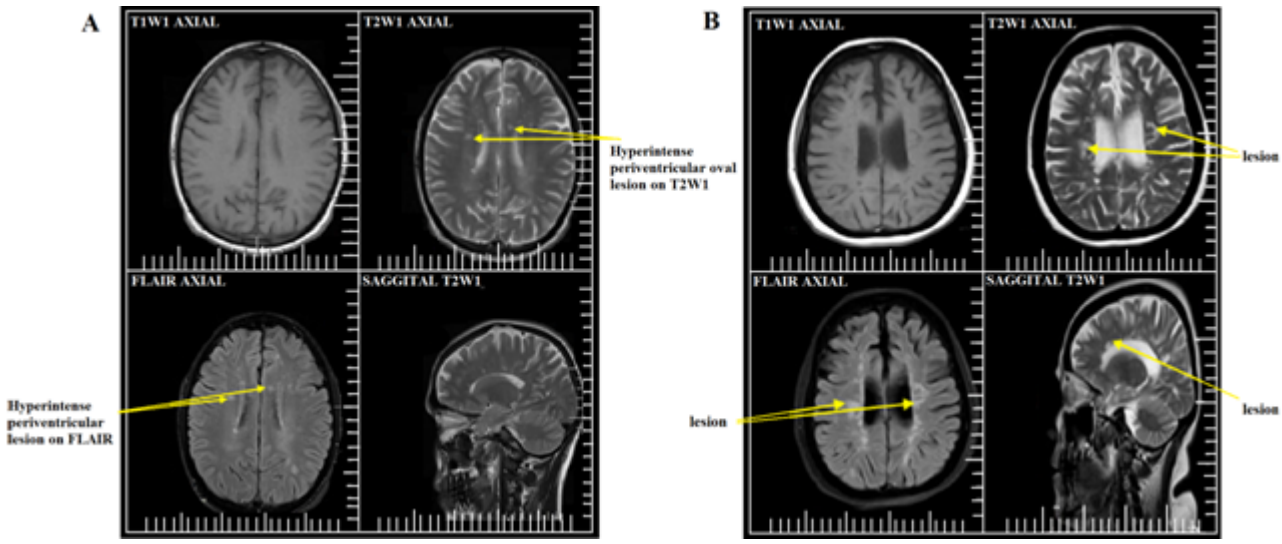

Figure 1. (**A**) A 29-year-old male patient: axial T1-weighted imaging (WI), T2WI, fluid-attenuated inversion recovery (FLAIR) imaging, and sagittal T2WI showing oval shaped white matter periventricular lesions; (**B**) a 38-year-old female patient: axial T1WI, T2WI, FLAIR, and sagittal T2WI showing oval shaped white matter periventricular lesions (Philips Achieva 1.5 T Nova Dual system)

Table 4. Detection of multiple sclerosis plaques by magnetic resonance imaging

Sequences	Lesions detected
T1W1	47
T2W1	99
Flair	100

Table 5. Distribution of multiple sclerosis plaques in brain parenchyma

	No of lesions	
	Mean	Standard deviation
Temporal lobe (n = 9)	0.2	0.63
Juxtacortical (n = 62)	13.1	9.20
Periventricular (n = 96)	0.1	–
Corpus callosum (n = 2)	13.7	9.33
Infratentorial (n = 16)	0.7	2.65
Temporal (n = 8)	1.5	2.28
Paraventricular (n = 97)	12.5	9.91
Parahippocampus (n = 4)	13.9	9.25
Acute (n = 82)	0.0	–

n = number of multiple sclerosis plaques

Discussion

Fatigue was rarely listed as a symptom of MS in studies performed before the 1980s [20]. In 1984, this scenario was changed [21]. The investigators published a detailed report in which 78% of 656 patients with MS surveyed, listed muscle fatigue as one of their symptoms. This report was striking only because fatigue was a common symptom in these patients interfering normal activities of life. However, the report was markedly different from previous reports [21]. Muscle fatigue was a clinical presentation in 19 patients in the present study (**Table 2**).

MS is the most common demyelinating disease in western world. Norway has the highest prevalence of MS with a female-to-male ratio 2.2:1 [22], while this ratio is 3.2:1 in Canada [23]. In the present study, there were 57 women and 43 men with MS, a ratio of 1.3:1 that shows slightly more involvement of men than in other countries. However, we establish that MS commonly presents in Pakistani women, but this ratio is relatively smaller. The present study shows less sex difference than western studies possibly because of social, cultural, and environmental factors that favor men.

In Canada, age of onset of MS appears variable. The mean age of onset of MS is about 30 years, and the peak age of onset is 23–24 years. Approximately 70% of cases arise between the ages of 20 and 40 years [23]. In the United Kingdom, age range is usually 20 to 50 years but cases in those >50 years of age have also been diagnosed [24]. In current study, the minimum age was 18 years, while maximum age of patients was 65 years. Our findings about the age of patients are not consistent with data of UK and Canada because average age of onset is less than 30 years in those populations, but in the Pakistani population it is more than 30 years, possibly a consequence of recognition and awareness of a problem by the patient.

MS lesions were mainly found in the deep white matter of CNS brain parenchyma, i.e. brain and spinal cord. One study of 249 patients demonstrated that white matter lesions and deep gray matter atrophy are spatially related. Their results are best compatible with the hypothesis that white matter lesions contribute to deep gray matter atrophy through axonal pathology [25]. While another suggests that subcortical gray matter abnormalities are seen with white matter plaques and atrophy, and brain atrophy is not related to microstructural changes of subcortical gray matter in MS [26]. In the present study, deep white matter lesions were present in 95 of the 100 cases

and juxtacortical lesions were observed in 62 patients as consistent with other studies in this respect (**Table 1**).

Conventional MR sequences are still widely used for the diagnosis of MS in the presence of newer techniques like MR spectroscopy and diffusion tensor imaging [27]. Quantification of the degree of atrophy seen by using T1W MR sequences provides an estimate of the magnitude of the most destructive aspects of MS. However, early detection of MS lesions on T1W sequences is limited [28]. In the present study, T1W sequences similarly had limited role in detection of MS plaques. T2W sequences provided better detection of demyelinating plaques and axonal injuries [29]. In the present study, MS lesions were more frequently detected on T2W sequence than T1 weighted sequences (**Table 4**). In the past decade, FLAIR has become a part of imaging guidelines and protocol for diagnosis of inflammatory brain lesions such as found in MS because of better detection of supratentorial, juxtacortical, and periventricular white matter brain lesions because of attenuation by the cerebrospinal fluid (CSF) [30]. In the present study, FLAIR sequence was most accurate and 100% of the lesions were detected using this sequence. Double-inversion-recovery imaging was established because of much better attenuation of both white matter lesion and CSF [31]. An increase of 53.8% in sensitivity has been reported with double-inversion-recovery as compared with T2W spin-echo imaging [32]. In the present study, the sensitivity of T2W and FLAIR sequences were similar to that of double-inversion-recovery imaging.

The distribution of MS plaques in brain is variable as suggested by previous studies [33], while in the present study, MS plaques were present in temporal lobe, and juxtacortical lesions were seen in 62%. Most lesions were detected in the periventricular region. These lesions were more common in supratentorial locations and in infratentorial locations, including posterior fossa and spinal cord (**Table 1**).

Spasticity is a common symptom of MS. Muscle spasms can belong to one of the two categories. Other clinical symptoms include paresthesia, numbness, and ataxic gate [34]. In the present study, 9 patients presented with ataxic gait, 3% slurred speech. However, numbness and paresthesia remained the more common presentations (**Table 2**). The functional abnormality leading to sensorimotor disability is associated with diseases of the spinal cord [35]. These diseases of spinal cord are evaluated by using conventional and advanced techniques, in which properties are linked to global disability measures such as the MS functional composite [36]. In the present study, 21 cases showed positive dorsal column signs. One of the clinical presentations is vision problems; 57 patients presented with vision disturbance, amongst which blurring of vision was observed in 48 (**Table 2**).

MS has a tendency to run in families and previous studies suggest that siblings of patients suffering from this disease have higher risk of developing it [37]. In the present study, 20 patients gave a positive history of similar white matter disease. A meta-analysis found white matter lesions associated with cognitive function in a large population-based sample of middle-aged adults [38]. White matter lesions associated with cognitive deficits is not unusual. Although the effect sizes were relatively small, the exact location of the lesions does impact on the afferent and efferent pathways controlling function [39]. In the present study, 70 patients presented with psychosomatic effects, e.g. sensory or motor system problems; and 54 patients had musculoskeletal problems, e.g. hemiparesis or monoparesis (**Table 2**); 2 patients had genitourinary symptoms.

Most previous studies were conducted in Europe and North America where diagnostic facilities such as MRI is widely available. To our knowledge, no data has been previously from Pakistan. Globally, MS has higher incidence in high income countries as compared to developing countries, which shows an association with socioeconomic status, but in our study, no such association was observed (**Table 3**). Low socioeconomic status was found to have a protective effect on MS [40]. However, association does not imply a causal effect and the relationship may be the result of reduced recognition in poorer patients.

T2W and FLAIR sequences of conventional MRI assist the detection of MS plaques. The present study is an early milestone in the early detection and creation of awareness among doctors and young and middle-aged adults with nontraumatic disability in Pakistan.

Lack of awareness among the population and lack of availability of diagnostic facilities in most parts of Pakistan and surrounding regions contribute towards factors leading to difference of the age of presentation. Sensorimotor impairment is variable, but predominant presentations in the present study population include numbness, musculoskeletal weakness, and blurring of

vision. Incidence of MS is increasing, possibly because of changes in life style in our region, for example, sedentary lifestyle, eating and dietary habits, and less sun exposure, particularly in women. MS is more common in women. In young to middle-aged individuals any degree of symptoms related to motor system weakness, particularly in females, should be considered as a demyelinating disease like MS. Familial tendency, older age, and male sex were found to have protective effect for the risk of MS, while no association is observed with socioeconomic status.

Recommendations

1. MRI should be performed with focus on temporal lobes having emphasis on periventricular and parahippocampus regions in particular.
2. T2WI and FLAIR sequences acquired on MRI should be given prime importance for detection of multiple sclerosis plaques.
3. Diagnostic facilities like MRI should be readily available. Proper training of neuroradiologist and neurophysicians should be provided.
4. Awareness to the general population should to be generated, with special emphasis on middle-aged patients with cognitive impairment including learning disabilities, loss of memory, and musculoskeletal weakness, and vision problems. Awareness of exercise, sun exposure, and healthy lifestyle should be promoted.
5. The medical community should be aware of middle-aged patients with clinical suspicion of MS, particularly those developing psychosomatic, musculoskeletal, and genitourinary symptoms without any obvious pathologic cause. They should be immediately assessed by neurophysicians in collaboration with neuroradiologists.
6. Patients having idiopathic cognitive impairment, musculoskeletal weakness, fatigue, incoordination of movements and vision problems should be considered for MRI.
7. A multidisciplinary approach with physiotherapy, occupational therapy, speech and language therapy, and neurorehabilitation, all integrated, is important in management of MS patients especially when they are accumulating significant disability.

Conflict of interest statement

The authors declare that there is no conflict of interest in this research.

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