SPECTRUM OF ACQUIRED DEMYELINATING DISORDERS OF THE CENTRAL NERVOUS SYSTEM IN ADULTS IN A TERTIARY CARE HOSPITAL

Muhammad Athar Javed[1], Dr Qamar Zaman[2], Dr Naveed Alam[3], Ather Enam[4]
Associate Professor Neurology[1], Postgraduate resident in Neurology[2-3]
Department of Neurology, King Edward Medical University / Mayo Hospital, Lahore

Correspondence to: Athar Javed, E mail: dratharjaved@hotmail.com

Background: Acquired demyelinating disorders of the central nervous system are diverse group of conditions characterized by destruction or disturbance of myelin sheath in the central nervous system i.e. brain and spinal cord. These vary in their causes, clinical presentations, and prognosis. **Objective:** To study the spectrum of acquired demyelinating disorders of central nervous systemin adults in a tertiary care hospital of Pakistan. **Materials and Methods:** This is a retrospective cross sectional descriptive study carried out at department of Neurology, King Edward Medical University/ Mayo hospital, Lahore. Study period was one year from March 2012 till February 2013. Medical records of the patients with history of focal or multifocal neurological deficits suspected of demyelinating disorders were reviewed. Those fulfilling the diagnostic criteria for specific demyelinating disorder were included in the study. Clinical, laboratory and radiological features were recorded on a specific proforma designed for the study. Results were analyzed using SPSS version 17. **Results:** During this period seventy one patients with various demyelinating disorders were diagnosed. There were 39 (55%) males and 32(45%) females with M: F ratio of 1.2:1.The mean age at presentation was29.5+ 9.3 years. Thirty four (48%) patients were diagnosed as clinically isolated syndrome (CIS), 23(32%) as multiple sclerosis (MS), 8(11.2%) as neuromyelitis optica (NMO), and 2(2.8%) as acute disseminated encephalomyelitis (ADEM). There was one case (1.5%) of each of the following disorders: progressive multifocal leukoencephalopathy (PML); vitamin B12 deficiency with dorsal myelopathy; post cardiac arrest hypoxic/ischemic symmetrical demyelination affecting basal ganglia; and central pontine myelinolysis (CPM). Out of the 34 cases of CIS, 17(50%) cases presented as transverse myelitis, 14(41%) optic neuritis, 2(6%) cerebellitis, and 1(3%) mutlifocal CIS. Among 23 cases of multiple sclerosis, 17(74%) had relapsing and remitting course (RRMS), 4(18%) primary progressive (PPMS), and 2(9%) secondary progressive course (SPMS). **Conclusion:** Demyelinating disorders are not uncommon in our local population. Inflammatory demyelinating disorders are more common than non-inflammatory causes. Monofocal clinically isolated syndrome (CIS) remained the most common form of inflammatory demyelination especially transverse myelitis followed by optic neuritis. Frequency of relapsing remitting multiple sclerosis was 74% and neuromyelitis optica was 11.2% in our local population. ADEM was rare (< 2.8%) in our adults population.

KEY WORDS: Clinically isolated syndrome (CIS), multiple sclerosis (MS), neuromyelitis optica (NMO), acute disseminated encephalomyelitis (ADEM), progressive multifocal leukoencephalopathy (PML)

INTRODUCTION

The term demyelination describes a loss of myelin with relative preservation of axons.[1] The etiology of acquired demyelinating disorder is multi-factorial.[1] However, traditionally known major group in this category comprised of immune mediated inflammatory demyelination with resultant wide spectrum of clinical syndromes such as multiple sclerosis (MS) and acute disseminated encephalomyelitis (ADEM).[2-7] Other less common causes of acquired demyelinating disorders include infections (such as progressive multifocal leukoencephalopathy), drugs and toxins (such as tin, lead, isoniazid and radiation), nutritional deficiencies (such as B12 deficiency), and acquired metabolic disturbances (such as osmotic demyelination causing pontine and extra-pontine myelinolysis).[8-12] These demyelinating disorders are recognized by their clinical presentation which may be monofocal or multifocal onset, course such as monophasic or polyphasic/relapsing, and specific neuro-imaging features of brain and spinal cord. Other investigations such as cerebrospinal fluid analysis, serum electrolytes, serum B12 and toxic screening may help in reaching the correct diagnosis.[13,14] Consensus definitions and criteria are available for the diagnosis of most inflammatory demyelinating disorders such as MS,ADEM and NMO.[15-17] We undertook this study to find out the spectrum of acquired demyelinating disorders of central nervous system in adults in a tertiary care hospital of Pakistan.

MATERIALS AND METHODS

This is a retrospective cross sectional descriptive study carried out at department of Neurology, King Edward Medical

University/Mayo hospital, Lahore. Study period was one year from March 2012 till February 2013. Medical records of the patients with history of focal or multifocal neurological deficits suspected of demyelinating disorders were reviewed. Inclusion criteria were: age >13 years; both sexes (male and female) and; symptoms/signs and MRI findings consistent withan acquired demyelinating disorder. Multiple sclerosis was diagnosed according to revised McDonald's diagnostic criteria 2010.[16]Clinically isolated syndrome (CIS) was defined as first acute clinical episode of CNS symptoms (without encephalopathy) with a presumed inflammatory demyelinating cause without any prior history of a demyelinating event.CIS was further classified into monofocal onset when the symptoms localized to a single site in CNS such as optic neuritis, transverse myelitis, isolated hemiplegic syndrome etc and multifocal onset when the symptoms localized to multiple CNS sites but without history of encephalopathy and fever. Neuromyelitis optica was diagnosed according to the revised diagnostic criteria by Wingerchuk et al. (2006). [17] Acute disseminated encephalomyelitis (ADEM) was diagnosed and classified according to International Pediatric MS Study Group-Consensus Definitions criteria with multifocal CNS white matter involvement associated with encephalopathy. Progressive multifocal leukoencephalopathy (PML) was diagnosed on the basis of clinical history, evidence of immunosuppresion, and MRI findings suggestive of PML. Central pontine and extrapontinemyelinolysis was diagnosed with evidence of white matter lesion on MRI brain in the setting of severe hyponatremia and its rapid correction. Exclusion criteria included: (1) age<13 years; (2) Ischemic demyelination (i.e. lacunar infarcts, Biswegner's disease and age related periventricular ischemic leukoencephalopathy; (3) Radiation induced white matter lesions; (4) Reversible posterior leukoencephalopathy syndrome (RPLS); and (5) Leukodystrophy. Those fulfilling the diagnostic criteria for specific demyelinating disorder were included in the study. Clinical, laboratory and radiological features were recorded on a specific proforma designed for the study. Results were analyzed using SPSS version [17].

RESULTS

During this period seventy one patients with various demyelinating disorders were diagnosed. There were 39 (55%) males and 32(45%) females with M: F ratio of 1.2:1. The mean age at presentation was 29.5+ 9.3 years. Thirty four (48%) patients were diagnosed as clinically isolated syndrome (CIS), 23(32%) as multiple sclerosis (MS), 8(11.2%) as neuromyelitis optica (NMO), and 2(2.5%) as acute disseminated encephalomyelitis (ADEM) {Table 1}. There was one case (1.5%) of each of the following disorders: progressive multifocal leukoencephalopathy (PML); vitamin B12 deficiency with dorsal myelopathy; post cardiac arrest hypoxic/ischemic symmetrical demyelination affecting basal ganglia; and central pontine myelinolysis (CPM). Out of the 34 cases of CIS, 17 (50%) cases presented as transverse myelitis, 14(41%) optic neuritis, 2(6%) cerebellitis, and 1(3%) mutlifocal CIS (Table 2). Among 23 cases of multiple sclerosis, 17(74%) had relapsing and remitting course (RRMS), 4(18%) primary progressive (PPMS), and 2(9%) secondary progressive form (SPMS) {Table 3}.

Table 1. Spectrum of demyelinating disorders (N=71)

Diagnosis of demyelinating disorder	Frequency n (%)	Males n (%)	Females n (%)	M:F
C.I.S	34 (48)	21 (61),	13 (39)	1.6:1
MS	23 (32)	11 (48)	12 (52)	1 : 1
NMO	08(1 1.2)	03(37.5)	05(62.5)	1:2.6
ADEM	02(2.8)	01(50)	01(50)	1:1
PML	01(1.5)	01(100)	0	1:0
B12 deficiencydorsal cord demyelination	01(1.5)	01(100)	0	1:0
Osmotic demyelination (CPM)	01(1.5)	01(100)	0	1:0
Hypoxic/ischemic demyelination	01(1.5)	0	01(100)	0:1

CIS, clinically isolated syndrome; MS, multiple sclerosis; NMO, neuromyelitis optica; ADEM, acute disseminated encephalomyelitis; PML= progressive multifocal leucoencephalopathy

DISCUSSION

This is the first study from Pakistan addressing the whole spectrum of acquired demyelinating disorders (inflammatory and non-inflammatory) of the central nervous system in adults. In our study the mean age at presentation was 29.5+ 9.3 with F: M ratio of 1.2:1.In a prospective, population-based sample of 1424 patients with multiple sclerosis in South-East Wales, the age at onset was 31. 2 years in male, 29.3 in female and F:M ratios were highest <16 years of age and declined with increasing age, with a male excess in those over 50.18 In our study the most common form of acquired demyelinating disorder was inflammatory demyelination. More over, the most common form of inflammatorydemyelination was CIS (50%) followed by multiple sclerosis (34%) and ADEM (2.5%). In comparison,Wu J.S etal. in their study retrospectively reviewed 842 cases over 12 years and showed that MS was the most common demyelinating disorder (83.5%) followed by CIS (10.9%) and ADEM (1.9%).19The high incidence of CIS in our study may be due to short period of review which was one year. With longer follow up some of the CIS cases may show conversion to definite MS or NMO as studies has shown that 30 to 70% of persons experiencing CIS later develop MS.20 In a Dutch study on acquired demyelinating disorder (ADS) in children, most patients presented with polyfocal ADS without encephalopathy (30%), followed by polyfocal ADS with encephalopathy (24%), optic neuritis (ON, 22%), monofocal ADS (16%), transverse myelitis (3%), and neuromyelitis optica (3%).21In our study, most common presentation of CIS was monofocal with transverse myelitis in 50% of casesfollowed by optic neuritis (41.2%) and cerebellitis (5.9%) respectively. In our study frequency of polyfocal CIS was only 2.9%. The most common presentations of acquired demyelination of the CNS in Canadian children were optic neuritis (ON; n = 51, 23%), acute disseminated encephalomyelitis (ADEM; n = 49, 22%), and transverse myelitis (TM; n = 48, 22%).22 Most common type of MS, according to the course of disease, was relapsing and remitting form (74%) in our study. This is slightly lower than previously reported (80-85%). 23In contrast, the frequency of primary progressive MS was 18% in our study which is in accordance with previous reports (15-20%). 24 The frequency of NMO was 11.8% in our study which is generally considered a rare disease in white populations and occurs much more commonly in nations with a predominately nonwhite population. The frequency of NMO was 6.8% in São Paulo and 20.5% in Rio de Janeiro, and mainly seen in persons of African descent in a Brazilian multiple sclerosis (MS) survey performed from 1995-1998. 24 Selective involvement of the optic nerves and spinal cord has been reported up to 15-40% from Japan and 36% from Hong Kong.25, 26 In contrast, in countries consisting predominately of a white population, NMO comprised less than 2% of all demyelinating disorders.18 F:M ratio was 2.6 : 1 in our study but much higher preponderance in female up to 9:1 in relapsing form of NMO has been reported. 27 The other types of acquired non inflammatory demyelinating disorders were rare in our study. To our knowledge there has been no published study till to date addressing the overall spectrum of acquired demyelinating disorders in adults with inclusion of both inflammatory and non-inflammatory causes of demyelination.

Table 2. Frequency of various presentations of clinically isolated syndrome (n=34)

Diagnosis	Frequency of CIS (n=34) n(%)	Overall frequency of demyelinating disorders (n=71) n(%)
Transverse Myelitis	17(50%)	17(24%)
Optic Neuritis	14(41.2%)	14(20%)
Cerebellitis	02(5.9%)	02(2.8%)
Multifocal	01(2.9%)	01(1.4%)

CONCLUSION

In conclusion, the demyelinating disorders are not uncommon in our local population. Inflammatory demyelinating disorders are more common than non-inflammatory demyelination. Monofocal CIS remained most common form of inflammatory demyelination especially transverse myelitis followed by optic neuritis. Frequency of RRMS was 74% and NMO 12% in our local population. ADEM was rare (< 2.5%) in our adults population. However, larger studies over longer period are required to confirm these findings and to observe the further conversion of CIS cases into MS or NMO.

Table 3. Frequency of various types of multiple sclerosis (n=23)

Types of MS	Frequency n (%)	Males n (%)	Females n (%)	M:F
RRMS	17(74)	08 (47),	09 (53)	1.1:1
PPMS	04 (18)	03(75)	01(25)	3 :1
SPMS	02(8)	0	02(100)	0:2

REFERENCES

1. Love S. Demyelinating diseases.J ClinPathol. 2006; 59(11): 1151–1159.
2. Weiner H L. Multiple sclerosis is an inflammatory T-cell-mediated autoimmune disease. Arch Neurol 2004;61:1613-5.
3. Lucchinetti C, Bruck W, Parisi J. et al Heterogeneity of multiple sclerosis lesions: implications for the pathogenesis of demyelination. Ann Neurol 2000; 47:707–717.
4. Lucchinetti CF, Mandler RN, McGavern D, et al. A role for humoral mechanisms in the pathogenesis of Devic'sneuromyelitisoptica. Brain 2002;125:1450–61.
5. Wingerchuk DM, Weinshenker BG. Neuromy elitis optica. Curr Treat Options Neurol 2005;7:173–82
6. Gupte G, Stonehouse M, Wassmer E, et al. Acute disseminated encephalomyelitis: a review of 18 cases in childhood. J Paediatr Child Health 2003;39:336–42.
7. Jones CT. Childhood autoimmune neurologic diseases of the central nervous system. NeurolClin 2003;21:745–64.
8. Thurnher MM, Thurnher SA, Muhlbauer B, et al. Progressive multifocal leukoencephalopathy in AIDS: initial and follow-up CT and MRI. Neuroradiology 1997;39:611–18
9. Hammarin AL, Bogdanovic G, Svedhem V, et al. Analysis of PCR as a tool for detection of JC virus DNA in cerebrospinal fluid for diagnosis of progressive multifocal leukoencephalopathy. J ClinMicrobiol 1996;34:2929–32.
10. Ginsberg MD, Hedley-Whyte ET, Richardson EP Jr. Hypoxic-ischemic leukoencephalopathy in man. Arch Neurol 1976;33:5–14
11. Karp BI, Laureno R. Pontine and extrapontine myelinolysis: a neurologic disorder following rapid correction of hyponatremia. Medicine (Baltimore) 1993;72:359–73.
12. Lampl C, Yazdi K. Central pontine myelinolysis. EurNeurol 2002;47:3–10.
13. Bergamaschi R, Tonietti S, Franciotta D, et al. Oligoclonal bands in Devic's neuromyelitis optica and multiple sclerosis: differences in repeated cerebrospinal fluid examinations. MultScler 2004;10:2–4.
14. Leake JA, Albani S, Kao AS, et al. Acute dissemi nated encephalomyelitis in childhood: epidemio logic, clinical and laboratory features. Pediatr Infect Dis J 2004;23:756–64.
15. Krupp Lauren B, Banwell B, and Tenembaum S for the International Pediatric MS Study Group. Neurology2007; 68(16): pp S7–S12
16. Polman CH, Reingold SC, Banwell B, et al. Diagnostic criteria for multiple sclerosis: 2010 Revisions to the McDonal criteria. Ann Neurol 2011; 69 (2): 292-30
17. D. M. Wingerchuk, W. F. Hogancamp, P. C. O'Brien, and B.G. Weinshenker, "The clinical course of neuromyelitisoptica (devic's syndrome)," Neurology 1999; 53(5): 1107–1114.
18. Cossburn M, Ingram G, Hirst C, Ben-Shlomo Y, Pickersgill TP, Robertson NP. Age at onset as a determinant of presenting phenotype and initial relapse recovery in multiple sclerosis. MultScler. 2012;18(1):45-54
19. J. S. Wu, M. N. Zhang, W. M. Carroll, and A. G. Kermode, "Characterisation of the spectrum of demyelinating disease in western Australia," Journal of Neurology, Neurosurgery and Psychiatry2008;79(9):1022–1026
20. Miller D, Barkhof F, Montalban X, Thompson A, Filippi M. "Clinically isolated syndromes sugges tive of multiple sclerosis, part I: natural history, pathogenesis, diagnosis, and prognosis". Lancet 2005;Neurol 4 (5): 281–8.
21. I.A.Ketelslegers, C. E. Catsman-Berrevoets, R. F. Neuteboom, M. Boon, K. G. J. van Dijk, Incidence of acquired demyelination of the CNS in Dutch children: a nationwide study.JNeurol 2012;259(9):1929-1935
22. Banwell B, Kennedy J, Sadovnick D, Arnold DL, Magalhaes S, et al. Incidence of acquired demy elination of the CNS in Canadian children. Neurology 2009 ;72(3):232-9.
23. Compston A, Coles A. "Multiple sclerosis". Lancet 2002; 359 (9313): 1221–31

24. Compston A, Coles A. "Multiple sclerosis". Lancet 2008; 372 (9648): 1502–17
25. Papais-Alvarenga RM, Vasconcelos CC, Alves-Leon SV, Batista E, Santos CM, Camargo SM, et al. The impact of diagnostic criteria for neuromy elitis optica in patients with MS: a 10-year follow-up of the South Atlantic Project. MultScler 1352458513495580, first published on August 22, 2013 as doi: 10.1177/1352 458513 495580
26. J. I. Kira, "Multiple sclerosis in the Japanese population"Lancet Neurology 2003; 2(2): 117–127.
27. K. K. Lau, L. K. Wong, L. S. Li, Y. W. Chan, H. L. Li, and V. Wong, "Epidemiological study of multi ple sclerosis in Hong Kong Chinese: question naire survey," Hong KongMedical Journal 2002; 8(2):77–80.