Multiple Sclerosis

39

Contents

Abstract

Multiple sclerosis (MS) is a chronic inflammatory demyelinating disease. The usual age of onset is between 20 and 40 years. Late-onset multiple sclerosis (LOMS) is defined as the first presentation of clinical symptoms occurring after the age of 50 years. The two groups 'adult-onset' multiple sclerosis (AOMS) and 'late-onset' multiple sclerosis (LOMS) defer in their demographic, clinical characteristics, disease course and response to treatment. Multiple sclerosis is extremely protean in its expression and severity. Based on the clinical course, MS has been categorized into (i) relapsing remitting MS (RRMS), (ii) secondary progressive MS (SPMS), (iii) primary progressive MS (PPMS) and (iv) progressive-relapsing (PRMS). About 80% of LOMS are affected by PPMS. About 94% of the patients with AOMS had RRMS. The diagnosis is based on careful clinical evaluation of the patient with investigations including MRI, CSF and evoked potentials. Treatment can be divided into treatment of the relapses, long-term immunomodulatory treatment and symptomatic relief. Patients often require care from a multidisciplinary team of healthcare providers.

Keywords

Multiple sclerosis · Adult-onset multiple sclerosis · Late-onset multiple sclerosis

Introduction

Multiple sclerosis (MS) is a chronic inflammatory demyelinating disease [1] affecting the optic nerves, brain stem and spinal cord [2–4], and in all probability, it is an autoimmune disease [1, 5, 6]. The usual age of onset is between 20 and 40 years in about 70% of the patients [7]. It rarely occurs before 10 years but can occur as late as 67 years [7]. Onset of MS at the age of 81 years

N. Nagaratnam et al., *Geriatric Diseases*,
https://doi.org/10.1007/978-3-319-33434-9_36

has been reported in a recent cohort study [8]. It is significantly greater in women than in men [3]. The pathogenesis is unclear, a complex interplay among genetic susceptibility and environmental triggers [6, 7, 9], and sex hormones [10, 11] have been implicated leading to immune dysregulation. Current research supports an immunologic and viral pathogenesis [5]. Several observations such as high EBV antibody levels, universal EBV seropositivity and alterations in EBV-specific CD8(+) T-cell immunity among others implicate Epstein-Barr virus (EBV) in the pathogenesis [12].

Late-onset multiple sclerosis (LOMS) is defined as the first presentation of clinical symptoms occurring after the age of 50 years [13–15], and the prevalence ranges between 4% and 9.6% in different studies [13]. In a study of 640 MS patients, 30 (4.6%) was diagnosed as late-onset MS, ranging 50–62 years [14]. In another population study of 1417 MS, 3.4% had their first symptoms at 50 years or older [16]. The two groups 'adult-onset' and 'late-onset' differ in their demographic, clinical characteristic, disease course and response to treatment [15]. LOMS is three times more common in women than in men [17].

Clinical Manifestations

Multiple sclerosis is extremely protean in its expression and severity [9]. It usually starts with an acute neurological disturbance termed 'clinically isolated syndrome' (CIS) [2, 18] which is the first clinical demyelinating event affecting the optic nerves, the brain stem or the spinal cord [2, 4]. It is mandatory that CIS should unequivocally be seen in MS, such as unilaterally optic neuritis, bilateral internuclear ophthalmoplegia, incomplete transverse myelitis or cerebellar syndromes [19]. About two-thirds of the patients follow a relapsing-remitting course [2], and half of them develop secondary progressive MS with disability [4], progressive deterioration without relapses or remissions [1]. The remaining third have a benign course with minimal or no disability [4]. It is possible to predict the subsequent development of MS in patients with CIS with MRI scan, and about 80% with abnormal MRI convert to MS compared to 20% with normal MRI [2]. An CIS presentation with normal MRI scan has a low risk of converting to MS [20, 21]. In some patients, 15–20% will have a primary progressive course [18]. Disease-modifying treatments can delay the development of MS in selected CIS patients with abnormal MRI [2, 4].

Based on the clinical course, MS has been categorized into (i) relapsing-remitting MS (RRMS), (ii) secondary progressive MS (SPMS), (iii) primary progressive MS (PPMS) and (iv) progressive-relapsing MS (PRMS). Recurrent attacks or relapses occur with RRMS which vary in frequency and severity and a steady baseline between relapses [3]. SPMS commonly follows RRMS or may develop slowly after an initial CIS [3]. About 10% of patients with MS have PPMS and affects older individuals with spinal cord involvement characterized by progressive weakness with spasticity of the lower limbs. PRMS is an uncommon subtype with gradual progressive course punctuated by one or more relapses [3]. A follow-up of over 25 years demonstrated similarities in the progressive phases of PPMS and SPMS although the two groups differ with respect to sex ratio [10].

About 80% of LOMS are affected by PPMS [8, 22], but when the disease phenotype is set, the progression is similar to AOMS [22]. In their study, 94% of the patients with AOMS had RRMS. Both groups had typical multifocal supratentorial lesions without significant differences [8]. In the same study, spinal lesions were more common in LOMS, but cerebellar lesions were less frequent compared to patients to AOMS so was gadolinium-enhanced lesions [8]. Differences and similarities between late-onset multiple sclerosis (LOMS) and adult-onset (AOMS) multiple sclerosis are shown in Table 1.

Diagnosis

There is no single test including MRI that is diagnostic [23]. As the patients get older, there is a tendency to relate the symptoms to ageing, thus

Table 1 Differences and similarities between late-onset multiple sclerosis (LOMS) and adult-onset (AOMS) multiple sclerosis

	Late onset	Adult onset
Age of onset	>50 years	<50 years
Gender (F:M)	1.73:1	3:1
Prevalence	4–9.6%	
Clinical patterns		
RRMS	50%	94%
PPMS	80%	
SPMS	35%	
Symptoms		
Motor	54–90%	60%
Spinal	60–81%	48%
Sensory, ataxia cognition	No difference	No difference
Cerebellar	Less common	Common
Laboratory		
CSF-oligoclonal binding	76%	
VEPs abnormal	81%	
MRI	60–80%	98%
Progression	Faster	
Prescription-DMD		
IFN-beta (reduced disability)	Not significant	Significant
Rate of exposure	Low	

Information sources: Kis et al. [8], Pollack et al. [14], Martinelli et al. [13], Shirani et al. [15], Delalande et al. [16]

leading to delayed or misdiagnosis. The diagnosis is based on careful clinical evaluation of the patient with investigations including MRI, CSF and evoked potentials [18], and according to the revised McDonald criteria, the diagnosis is based on the clinical course and MRI findings [6]. The revised McDonald criteria incorporated defined MRI criteria to dissemination in space (DIS) and dissemination in time (DIT). DIS is shown by one or more MRI-detected lesions typical of MS, and DIT is shown by a current (active) and previous (non-active) lesion. The requirements have been simplified in the recent revised 2015 McDonald criteria allowing an earlier diagnosis from a single gadolinium-enhanced MRI which can provide evidence for dissemination in space and time [23] if there are both silent enhancing and non-enhancing lesions [24]. Pathologically the lesions in the MRI are non-specific, and characteristic lesions that support MS include ovoid lesions, Dawson fingers, corpus callosum lesions and asymptomatic spinal cord lesions [23]. Gadolinium also helps to rule out alternate diagnoses in the brain such as neoplasm, vascular malformations and leptomeningeal disease and in the case of the spinal cord spinal stenosis or tumour [23].

Treatment

The two clinical processes, relapses and progression, influence the course of MS [25]. Interferon-beta, glatiramer acetate and mitoxantrone are three therapeutic agents found effective in large three-phase studies [26]. Treatment can be divided into treatment of the relapses, long-term immunomodulatory treatment and symptomatic relief [6]. Corticosteroids are used for treatment of relapses [9], intravenous methyl prednisolone for 3 days [1, 18]. For RRMS patients, the first-line disease-modifying agents are interferon-beta and glatiramer [18]. Interferon-beta reduces the frequency of attacks and the progression of disability in RRMS [1]. In patients with SPPMS, PPMS and worsening RRMS, mitoxantrone, an immunosuppressant administered intravenously, reduces neurologic disability and relapse frequency [27] and reduces worsening of RRMS and SPMS [28]. Symptomatic treatment includes management of spasticity, pain, urinary problems, depression and anxiety, paraesthesia and fatigue [1, 18]. Patients often require care from a multidisciplinary team of healthcare providers, and primary care providers must have basic knowledge of the disease [5].

Impact

In the Western countries, the average age of people living with MS is about mid-50s [29]. The prevalence of MS is increasing more so in the very elderly because of the increase in life expectancy and the commencement of effective treatments. Individuals with MS have multiple chronic

conditions together with increased mental comorbidities [30]. The quality of life of the patients and that of the carers is reduced [31]. Depression and anxiety are vastly prevalent symptoms of MS. Lifetime prevalence rate of depression in MS is approximately 50%, and it is a major predictor of morbidity, mortality, quality of life and suicide risks among others [32], and life stress is positively correlated with current and future depressive symptoms [33]. A study on the psychological impact of MS that the patient experiences is related to enhanced appreciation of life and increase in spiritual pursuits and benefit-finding which was related to higher levels of anxiety and anger and not to depression [34]. MS is associated with a number of functional deficits and progressive disability, and loss of mobility is the most disabling aftermath [35]. Secondary progression occurs on average after 19 years after an exacerbating remitting onset of MS, and the median time to reach limitation of ambulation is 8 years, walking with stick 20 years and wheelchair bound 30 years [35]. The age at clinical onset of MS is significant; for the younger the onset, the younger the age at assignment of disability milestones, and females reached the disability milestones at an older age [36]. In the elderly, the symptoms of MS may be compounded by multiple problems such as comorbidities and multiple medications (Box 1).

Box 1 Key Points: Multiple Sclerosis

Multiple sclerosis (MS) is a chronic inflammatory demyelinating disease [1] affecting the optic nerves, brain stem and spinal cord [2–4], and in all probability, it is an autoimmune disease [1, 5, 6].

It rarely occurs before 10 years but can occur as late as 67 years [7].

Multiple sclerosis is extremely protean in its expression and severity [9]. It usually starts with an acute neurological disturbance termed 'clinically isolated syndrome' (CIS) [2, 18] which is the first clinical demyelinating event affecting the optic nerves, the brain stem or the spinal cord [2, 4].

About two-thirds of the patients follow a relapsing-remitting course [2], and half of them develop secondary progressive MS with disability [4], progressive deterioration without relapses or remissions [1]. The remaining third have a benign course with minimal or no disability [4].

The two clinical processes, relapses and progression, influence the course of MS [25].

Treatment can be divided into treatment of the relapses, long-term immunomodulatory treatment and symptomatic relief [6].

Multiple Choice Questions

1. The following are true of multiple sclerosis (MS), EXCEPT:
   A. Current research supports an immunologic and viral pathogenesis.
   B. Adult-onset MS is three times more common in women than in men.
   C. It usually starts with an acute neurological disturbance termed 'clinically isolated syndrome' (CIS).
   D. About one-third of the patients follow a relapsing-remitting course.
2. The following are true, EXCEPT:
   A. Gadolinium also helps to rule out alternate diagnoses in the brain such as neoplasm, vascular malformations and leptomeningeal disease.
   B. Pathologically the lesions in the MRI are non-specific.
   C. Lifetime prevalence rate of depression in MS is approximately 20%.
   D. Interferon-beta reduces the frequency of attacks and the progression of disability in RRMS.

MCQs Answers

1 = D; 2 = C

References

1. Pender MP. Neurology.4:Multiple sclerosis. Med J Aust. 2000;172(11):556–62.
2. Brownlee WJ, Miller DH. Clinically isolated syndromes and the relationship to multiple sclerosis. J Clin Neurosci. 2014;21(12):2065–71.
3. Hurwitz BJ. The diagnosis of multiple sclerosis and the clinical subtypes. Ann Indian Acad Neurol. 2009; 12(4):226–230.
4. Miller DH, Chard DT, Ciccarelli O. Clinically isolated syndromes. Lancet Neurol. 2012;11(2):157–69.
5. Swain SE. Multiple sclerosis. Primary health care implications. Nurse Pract. 1996;21(7):40,43,47–50.
6. Simo M. Therapy of multiple sclerosis. Neuropsychopharmacol Hung 2009;11(1):23–6.
7. Redjak K, Jsckson S, Giovannoni C. Multiple sclerosis: a practical overview for clinicians. Brit Med Bull. 2010; 95(1):79–104.
8. Kisv B, Rumberg B, Berlet P. Clinical characteristics of patients with late-onset multiple sclerosis. J Neurol. 2008;255:697–702.
9. Lynch SG, Rose JW. Multiple sclerosis. Dis Mon. 1996;42(1):1–55.
10. Ebers GC. Natural history of primary progressive multiple sclerosis. Mult Scier. 2004; 10Suppl 1:S8–13.
11. Orton SM, Herrera BM,Yee IM, Valdar W, Ramagopalan SV,Sadovnick AD, et al. Sex ratio of multiple sclerosis in Canada: a longitudinal study. Lancet Neurol. 2006;5(11):932–936.
12. Pender MP, Burrows SR. Epstein-Barr virus and multiple sclerosis: potential opportunities for immunotherapy. Clin Transl Immunology. 2014;31(3):e27. https://doi.org/10.1038/cti.2014.25.eCollection 2014.
13. Martinelli V, Rodegher M, Moiola L, Comi G. Late-onset multiple sclerosis: clinical characteristics, prognostic factors and differential diagnosis. Neurol Sci. 2004;25Suppl 4:S350–5. (abstract).
14. Pollack ML, Barak Y, Achiron A. Late-onset multiple sclerosis. J Am Geriatr Soc. 2001;49(2):168–71.
15. Shirani A, Zhan Y, Petkan J, Gustafson P,Karom ME, Evans C, et al. Multiple sclerosis in older adults: The clinical profile and impact of interferon beta treatment. BioMEd Res International 2015 (2015). https://doi.org/10.1155/2015/451912.
16. Delalande S, De Seze J Ferriby D, Stojkovic T, Vermersch P. Late onset multiple sclerosis. Rev Neurol (Paris). 2002;158(11):1082–7.
17. Bove R, Healy BC, Augustine A, Gholipour T, Chitnis T. Effect of gender on late–onset multiple sclerosis. Research Gate. https://doi.org/10.1177/1352458512438236.
18. Tsang BK, Macdonell R. Multiple sclerosis-diagnosis, management and prognosis. Aust Fam Physician. 2011;40(12):948–55.
19. Swanton JK, Fernando KT, Dalton CM, Miszkiel KA, Thompson AJ, Plant GT, et al. Modification of MRI criteria for multiple sclerosis in patients with clinically isolated syndromes. J Neurol Neurosurg Psychiatry. 2006;77:830–3.
20. Tintore M, Riviera A, Rio J, Nos C, Grive E, Tellez N, et al. Baseline MRI predicts future attacks and disability in clinically isolated syndromes. Neurology. 2006;67:968–72.
21. Beck RW, Trobe JD, Moke PS, Gal RL, Xing D, Bhatti MT, et al. High-and low-risk profiles for the development of multiple sclerosis within 10 years after optic neuritis: Experience of the optic neuritis treatment trial. Arch Ophthalmol 2003;121:944–9.
22. Tramlett H, Devonshire V. Is late onset multiple sclerosis associated with worse outcome? Neurology. 2006;67:954–959.
23. Traboulsee AL, Li DK. The role of MRI in the diagnosis of multiple sclerosis. Adv Neurol. 2006;98:125–46.
24. Milo R, Miller A. revised diagnostic criteria of multiple sclerosis. Autoimmun. 2014;13(4–5):518–24.
25. Confavreux C, Vukusic S. The natural history of multiple sclerosis. Rev Pract. 2006;56(12):1313–20.
26. Bitsch A, Bruck W. Differentiation of multiple sclerosis. Subtypes. CNS Drugs. 2002;16(6):405–418.
27. Fox EJ. Management of worsening multiple sclerosis with mitoxantrone: a review. Clin Ther. 2006; 28(4):461–74.
28. Scott LJ, Figgitt DP. Mitoxantrone: a review of its use in multiple sclerosis. CNS Drugs. 2004;18(6):379–96.
29. Marrie RA, Yu J, Blanchard S, Leung S, Eliott L. The rising prevalence and changing age distribution of multiple sclerosis in Manitoba. Neurology. 2010; 74(6):465–471.
30. Simpson RJ, McLean G, Guthrie M, Mair E, Mercer SW. Physical and mental health comorbidity is common in people with multiple sclerosis: nationally representing cross-sectional population database analysis. BMC Neurology. 2014 https://doi.org/10.1186/1471-2377-14-128.
31. Opara J, Jaracz K, Brola W. Burden and quality of life in caregivers of persons with multiple sclerosis. Neurol Neurochir Pol. 2012;46(5):472–9.
32. Paparrigopoulos T, Ferentinos P, Kouzoupis A, Koutsis G, Papadimitriou GN. The neuropsychiatry of multiple sclerosis: focus on disorders of mood, affect and behaviour. Int Rev Psychiatry. 2010;22(1):14–21.
33. Aikens JE, Fischer JS,Namey M, Rudick RA. A replicated prospective investigation of life stress, coping and depressive symptoms in multiple sclerosis. J Behav Med. 1997;20(5):433–45.
34. Mohr DC. Dick LP, Russo D, Pinn J, Boudewyn AC, Likosky W, et al. The psychological impact of multiple sclerosis: exploring the patient's perspective. Health Psychol. 1999;18(4):376–82.
35. Dunn J. Impact of mobility impairment on the burden of caregiving in individuals with multiple sclerosis. Expert Rev Pharmacoecon Outcomes Res. 2010; 10(4):433–40. https://doi.org/10.1586/erp.10.
36. Confavreux C, Vukusic S. Age at disability milestones in multiple sclerosis. Brain. 2006;129(Pt3):595–605.