Recent progress in epidemiology, clinical features, and therapy of multiple sclerosis in China

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Abstract: Multiple sclerosis (MS) is a demyelinating disease of the central nervous system characterized by inflammation, demyelination, and neurodegeneration. It mainly affects young adults, imposing a heavy burden on families and society. The epidemiology, clinical features, and management of MS are distinct among different countries. Although MS is a rare disease in China, there are 1.4 billion people in China, so the total number of MS patients is not small. Because of the lack of specific diagnostic biomarkers for MS, there is a high misdiagnosis rate in China, as in other regions. Due to different genetic backgrounds, the clinical manifestations of MS in Chinese are different from those in the West. Herein, this review aims to summarize the disease comprehensively, including clinical profile and the status of disease-modifying therapies in China based on published population-based observation and cohort studies, and also to compare with data from other countries and regions, thus providing help to develop diagnostic guideline and the novel therapeutic drugs. Meanwhile, we also discuss the problems and challenges we face, specifically for the diagnosis and treatment of MS in the middle- and low-income countries.

Keywords: China, clinical features, epidemiology, multiple sclerosis, therapy

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Introduction

Multiple sclerosis (MS) is a classical inflammatory demyelinating disorder of the central nervous system (CNS), which commonly starts affecting young adults and lasting for a lifetime, leading to considerable social impact and economic burden.[1] It was earlier generally considered that MS mainly occurred in several parts of Europe and the United States as well as the high latitude regions. However, with the further improvement of diagnostic criteria increasing earlier diagnosis rate, a universal increase in the prevalence and incidence of MS in many regions has been reported during recent decades.[2,3] Till now, MS has been indicated to be a worldwide problem, with different prevalence and incidence across the globe.[4,5]

According to a report from the atlas of MS third edition, the number of people with MS across the globe has increased from 2.3 million in 2013 to 2.8 million in 2020.[6] An increasing number of studies have demonstrated that there are significant differences in MS in terms of epidemiology and clinical characteristic across diverse races and countries. At present, the cause of MS remains unclear; it is considered as a result of the complex interaction between genetic and environmental factors.[7] So far, no specific diagnostic biomarkers have found in MS, and it is difficult for early identification. MS was historically believed as a T-cell-mediated disease, and most disease-modifying therapies (DMTs) focused on eliminating these pathogenic T cells.[8] However, in recent years,

there has been a tremendous change in understanding the immune mechanism of MS, away from T-cell-centered dogma to a recognition that B cells play a core role in MS pathogenesis.[9] B-cell-depleting therapies upend the traditional idea of T-cell-based therapy and may play a crucial role in reducing relapses and delaying disability progress.[10] Although a dozen different DMTs have been approved for MS therapy globally, only six of them are available in clinical application of China until now. Therefore, there is a lack of data related to the currently available medications for MS and their efficacy and safety in China.

As the most populous country with wide geographical distribution in the world, so far, the comprehensive and accurate description of MS in China is insufficient, and the reason is the uneven development of medical diagnosis in various regions. To fill the gap, in this review, we collected 92 studies published in English and Chinese regarding MS in China from 2011 to July of 2022 and conducted further analysis of these data of MS, including the epidemiology, clinical features, treatment, and prognosis, and also to compare comprehensively the data of MS in China to those in other races and countries. This article mainly focuses on identifying the actual picture of MS in China and providing the basis for future studies in the middle- and low-income countries.

Search strategy and results

In this literature review, all available studies on MS in Chinese population published in China National Knowledge Infrastructure, Wanfang and PubMed databases from 2011 to July of 2022 were collected. The using search terms were [('Multiple Sclerosis' or 'MS') and ('China' or 'Chinese' or 'Hongkong' or 'Taiwan')]. The references of retrieved articles were also screened for avoiding missing potentially relevant studies. The types of studies included prospective, retrospective, cross-sectional, and case-control studies, and clinical trials, published in full-text with relevant information to extract. We did not collect the case reports, review articles, commentaries, and meta-analysis. Other papers with irrelevant or incomplete data were also excluded.

The initial search strategy identified 218 studies after reading abstract. After reviewing all retrieved articles by applying the above criteria, a total of 92 studies were cited in this review.[11–102] Of these 92 articles, 17 were reported in English, the resting 75 in Chinese. Of these selected studies, 87 were conducted in mainland China, 4 in Hong Kong, and 1 in Taiwan, including 15,653 patients. For studies reporting qualitative and quantitative data, available information on demographics, clinical features, treatment, and results were further integrated and tabulated. The basic characteristics of the Chinese MS cohort are summarized in Table 1.

Epidemiology

Prevalence and incidence

The prevalence and incidence of MS seem to be increasing globally. The estimated global prevalence and incidence of MS in 2020 were, respectively, 35.9/100,000 and 2.1/100,000. However, the reported epidemiological data of MS varied greatly in different regions and countries of the world, which might be related to genetic and environmental factors and poor medical data collections. The highest prevalence was reported mainly

Table 1. Demographics and clinical characteristics of MS patients in China.

MS features	Chinese cohort (n = 15,653)	References
Demographics		
Age, years	41.53 adult*; 8.05 children*	Ren and Qiao,[12] Wang,[15] Long et al.,[17] Han and Liu,[22] Wang,[25] Cheng et al.,[26] Ren et al.,[27] Li et al.,[28] Zhu et al.,[29] Duan,[30] Gong,[31] Jia,[32] Wang and Wei,[33] Chen,[34] Duan and Hua,[35] Kong,[36] Zhang,[37] He and Zou,[38] Liu and Huang,[39] Li and Zhou,[40] Xue,[50] Yang and Yang,[54] Zhang et al.,[59] Ruan,[63] Wang et al.,[65] Chen et al.,[66] Meng,[67] Zhou and Luo,[70] Bai,[75] Zhou and Fu,[77] Ouyang and Zhu,[78] Huang et al.,[79] Lin,[80] Shi,[82] Liu et al.,[87] Long et al.,[89] Liu et al.,[92] Chen et al.,[93] Zhang et al.,[95] Zhang et al.,[98] Xu et al.[101]

(Continued)

Table 1. (Continued)

MS features	Chinese cohort (*n* = 15,653)	References
F/M ratio	10,482/5171 (2.0)	Cui *et al.*,[11] Ren and Qiao,[12] Guo *et al.*,[13] Cheng and Li,[14] Wang,[15] Fan *et al.*,[16] Long *et al.*,[17] Liu and Feng,[18] Qian,[19] Li *et al.*,[20] Wang,[21] Han and Liu,[22] Zheng,[23] Wang *et al.*,[24] Wang,[25] Cheng *et al.*,[26] Ren *et al.*,[27] Li *et al.*,[28] Zhu *et al.*,[29] Duan,[30] Gong,[31] Jia,[32] Wang and Wei,[33] Chen,[34] Duan and Hua,[35] Kong,[36] Zhang,[37] He and Zou,[38] Liu and Huang,[39] Li and Zhou,[40] Qiu,[41] Lin *et al.*,[42] Song,[43] Lin *et al.*,[44] Zhao *et al.*,[45] Xu,[46] Liu *et al.*,[47] Zhu *et al.*,[48] Ma and Liu,[49] Xue,[50] Xie *et al.*,[51] Chen *et al.*,[52] Hu and Chang,[53] Yang and Yang,[54] Lu *et al.*,[55] Zhang,[56] Liu *et al.*,[57] Zhao *et al.*,[58] Zhang *et al.*,[59] Huang and Chen,[60] Su,[61] Hu,[62] Ruan,[63] Zeng *et al.*,[64] Wang *et al.*,[65] Chen *et al.*,[66] Meng,[67] Zhou and He,[68] Wu,[69] Zhou and Luo,[70] Zhang *et al.*,[71] He *et al.*,[72] Lv,[73] Li,[74] Bai,[75] Yin,[76] Zhou and Fu,[77] Ouyang and Zhu,[78] Huang *et al.*,[79] Lin,[80] Xing *et al.*,[81] Shi,[82] Wang,[83] Feng,[84] Han,[85] Chan *et al.*,[86] Liu *et al.*,[87] Chan *et al.*,[88] Long *et al.*,[89] Yang *et al.*,[90] Li *et al.*,[91] Liu *et al.*,[92] Chen *et al.*,[93] Liu *et al.*,[94] Zhang *et al.*,[95] Lu *et al.*,[96] Fang *et al.*,[97] Zhang *et al.*,[98] Zhao *et al.*,[99] Zheng *et al.*,[100] Xu *et al.*,[101] Zhao *et al.*,[102] Lai *et al.*[103]
Clinical course of MS		Guo *et al.*,[13] Fan *et al.*,[16] Zheng,[23] Ren *et al.*,[27] Gong,[31] Zhang,[37] Qiu,[41] Lin *et al.*,[42] Xu,[46] Ma and Liu,[49] Liu *et al.*,[57] Zhao *et al.*,[58] Zeng *et al.*,[64] Bai,[75] Ouyang and Zhu,[78] Li *et al.*,[91] Zhang *et al.*,[95] Zhao *et al.*[102]
RRMS (%)	85.2%	
SPMS (%)	8.6%	
PPMS (%)	6.2%	
Clinical manifestations		Cui *et al.*,[11] Guo *et al.*,[13] Wang,[15] Fan *et al.*,[16] Long *et al.*,[17] Liu and Feng,[18] Li *et al.*,[20] Wang,[21] Zheng,[23] Wang *et al.*,[24] Wang,[25] Cheng *et al.*,[26] Ren *et al.*,[27] Zhu *et al.*,[29] Duan,[30] Gong,[31] Jia,[32] Wang and Wei,[33] Chen,[34] Duan and Hua,[35] Zhang,[37] He and Zou,[38] Liu and Huang,[39] Li and Zhou,[40] Qiu,[41] Song,[43] Lin *et al.*,[44] Zhao *et al.*,[45] Ma and Liu,[49] Xue,[50] Xie *et al.*,[51] Chen *et al.*,[52] Hu and Chang,[53] Yang and Yang,[54] Lu *et al.*,[55] Liu *et al.*,[57] Zhao *et al.*,[58] Zhang *et al.*,[59] Huang and Chen,[60] Su,[61] Zeng *et al.*,[64] Wang *et al.*,[65] Meng,[67] Zhang *et al.*,[71] He *et al.*,[72] Bai,[75] Yin,[76] Ouyang and Zhu,[78] Huang *et al.*,[79] Lin,[80] Xing *et al.*,[81] Shi,[82] Feng,[84] Han,[85] Li *et al.*,[91] Liu *et al.*[92]
Optic neuritis (%)	1193/4865 (24.5)	
Limb weakness (%)	2070/4865 (42.5)	
Sensory disturbances (%)	1741/4865 (35.8)	
Sphincter dysfunction (%)	462/4865 (9.5)	
Ataxia (%)	688/4865 (14.1)	
Cognitive impairment (%)	202/4865 (4.2)	
Epilepsy (%)	33/4865 (0.7)	
Consciousness disturbance (%)	51/4865 (1.0)	
Cranial nerve involvement (%)	610/4865 (12.5)	
Eye movement-related nerves	518/4865 (10.6)	

(Continued)

Table 1. (Continued)

MS features	Chinese cohort (*n* = 15,653)	References
Facial weakness	27/4865 (0.6)	
Bulbar palsy	50/4865 (1.1)	
Comorbidity (%)		Liu and Feng,[18] Wang,[21] Zhang,[56] Liu *et al.*,[57] Ouyang and Zhu,[78] Feng,[84] Chan *et al.*[88]
Autoimmune diseases		
Systemic autoimmune diseases	37/496 (7.6)	
MG	10/496 (2.0)	
Nonautoimmune diseases		
Hypertension	59/496 (11.9)	
Coronary heart disease	20/496 (4.0)	
CSF study		
White cell count (>8 cells/ mm^3) (%)	260/1077 (24.1)	Wang,[15] Wang,[25] Cheng *et al.*,[26] Ren *et al.*,[27] Li *et al.*,[28] Zhu *et al.*,[29] Duan,[30] Gong,[31] Liu and Huang,[39] Zhao *et al.*,[45] Ma and Liu,[49] Xue,[50] Hu and Chang,[53] Yang and Yang,[54] Lu *et al.*,[55] Su,[61] Chen *et al.*,[66] Zhou and Luo,[70] Bai,[75] Ouyang and Zhu,[78] Huang *et al.*,[79] Lin,[80] Feng,[84] Han,[85] Long *et al.*[89]
Protein, g/L (interquartile range)	0.4–0.9	Wang,[15] Zheng,[23] Ren *et al.*,[27] Zhu *et al.*,[29] Zhu *et al.*,[48] Hu and Chang,[53] Yang and Yang,[54] Lu *et al.*,[55] Su,[61] Chen *et al.*,[66] Zhou and Luo,[70] Bai[75], Ouyang and Zhu,[78] Huang *et al.*,[79] Lin,[80] Feng,[84] Long *et al.*[89]
IgG index >0.7 (%)	193/456 (20.4)	Zheng,[23] Li *et al.*,[28] Wang and Wei,[33] Duan and Hua,[35] Lin *et al.*,[44] Xue,[50] Lu *et al.*,[55] Bai,[75] Yin,[76] Ouyang and Zhu,[78] Han,[85] Liu *et al.*[92]
OCB (%)	671/1380 (48.6)	Wang *et al.*,[24] Li *et al.*,[28] Duan,[30] Gong,[31] Jia,[32] Zhao *et al.*,[45] Hu and Chang,[53] Bai,[75] Chan *et al.*,[88] Long *et al.*,[89] Yang *et al.*,[90] Li *et al.*,[91] Liu *et al.*,[92] Lu *et al.*,[96] Zhao *et al.*[99]
MRI features		
Brain MRI abnormalities (%)		Cui *et al.*,[11] Guo *et al.*,[13] Wang,[15] Li *et al.*,[20] Zheng,[23] Ren *et al.*,[27] Li *et al.*,[28] Zhu *et al.*,[29] Duan,[30] Gong,[31] Jia,[32] Wang and Wei,[33] Duan and Hua,[35] Lin *et al.*,[42] Lin *et al.*,[44] Xu,[46] Zhu *et al.*,[48] Xue,[50] Hu and Chang,[53] Huang and Chen,[60] Hu,[62] Ruan,[63] Bai,[75] Yin,[76] Zhou and Fu,[77] Ouyang and Zhu,[78] Long *et al.*,[89] Zhao *et al.*[99]
Periventricular lesions	1061/1635 (64.9)	
Cortical lesions	633/1635 (38.7)	
Cerebellar lesions	197/1635 (12.0)	
Brainstem lesions	542/1635 (33.1)	Zheng,[23] Bai,[75] Ouyang and Zhu,[78] Long *et al.*[89]
Midbrain	24/209 (11.5)	
Pons	55/209 (26.3)	

(Continued)

Table 1. (Continued)

MS features	Chinese cohort (*n* = 15,653)	References
Medulla	27/209 (12.9)	
Spinal cord MRI abnormalities (%)	778/1267 (61.4)	Qian,[19] Jia,[32] Wang and Wei,[33] Liu *et al.*,[47] Xue,[50] Ruan,[63] Zhou and Fu,[77] Huang *et al.*,[79] Lin[80], Feng,[84] Yang *et al.*[90]
Cervical cord lesions	420/1267 (33.1)	
Thoracic cord lesions	224/1267 (17.7)	
Cervical and thoracic cord lesions	93/1267 (7.3)	
Lumbar cord lesions	19/1267 (1.5)	

Data are presented as *n* (%) or median [IQR].
*Average age.
CSF, cerebrospinal fluid; IgG, immunoglobulin G; MG, myasthenia gravis; MRI, magnetic resonance imaging; MS, multiple sclerosis; OCB, oligoclonal bands; PPMS, primary progressive MS; RRMS, relapsing-remitting MS; SPMS, secondary progressive MS.

in the Americas and Europe (117.49/100,000 and 142.81/100,000, respectively), while the lowest prevalence in Latin America (ranging from 2.0/100,000 to 69.0/100,000).[104] The reported prevalence of MS had a wide regional variation across Asia areas, ranging from 3 to 50 per 100,000 population, with the lowest levels reported in South East Asia (3.26/100,000).[105] Despite the difference in prevalence, recent studies have shown the obvious increase in prevalence in most regions, including some countries with low prevalence, such as Japan (18.6/100,000),[106] Korea (3.23/100,000),[107] and Pakistan (10.0/100,000).[108] The crude data across the globe can be available from the third edition of the Atlas of MS.[106]

Despite lack of national data to reveal the real prevalence and incidence of MS in China, the latest MS data published by Multiple Sclerosis International Federation showed that there were nearly 42,440 MS patients in China in 2020.[109] We collected the published original articles, of which most were based on a single center from different regions, to assess MS epidemiology. For example, a population-based survey covering 18 districts conducted by Ruijin Hospital showed a prevalence of 1.39/100,000 individuals in Shanghai in 2007.[110] In 2008, Lau *et al.*[111] reported the prevalence of 4.8 per 100,000 in Hong Kong. Recently, Xu *et al.*[101] published representative national data by using National Medical Insurance Databases with the prevalence of 2.44/100,000, which was smaller than the

reported from the third edition of the Atlas of MS with 3/100,000. The data showed that Liaoning Province had the highest prevalence with 3.13, followed by Zhejiang Province (2.89), Guangdong Province (2.66), Inner Mongolia Autonomous Region (2.38), and Chongqing Municipality (1.67).[101] Liu *et al.*[94] reported that the MS prevalence in Shandong Province was estimated to be 5.2/100,000 using hospitalized data. From these data, we could see that the prevalence of MS in China followed a geographic distribution. MS incidence increases with latitude and altitude in China.[112] Specifically, some regions with high-latitudes, like Inner Mongolia had higher incidence compared to mid-latitudes and low-latitudes. Also, the risk of MS in the low-altitude eastern regions was lower than the high-altitude Western regions. The published data on the prevalence, the incidence, and the sex ratio of MS in different provinces are presented in Figure 1. Due to low incidence rate of MS in China, it is considered as a rare disease in China; however, the total number of MS patients is not small due to 1.4 billion people in China.

Epidemiology
MS is more predominant in females, similar to other autoimmune diseases of the nervous system, such as neuromyelitis optica spectrum disorder (NMOSD) and autoimmune encephalitis.[113–115] Many retrospective studies demonstrated that the prevalence of MS in women was two to three times higher than that in men.[116–118] In some regions,
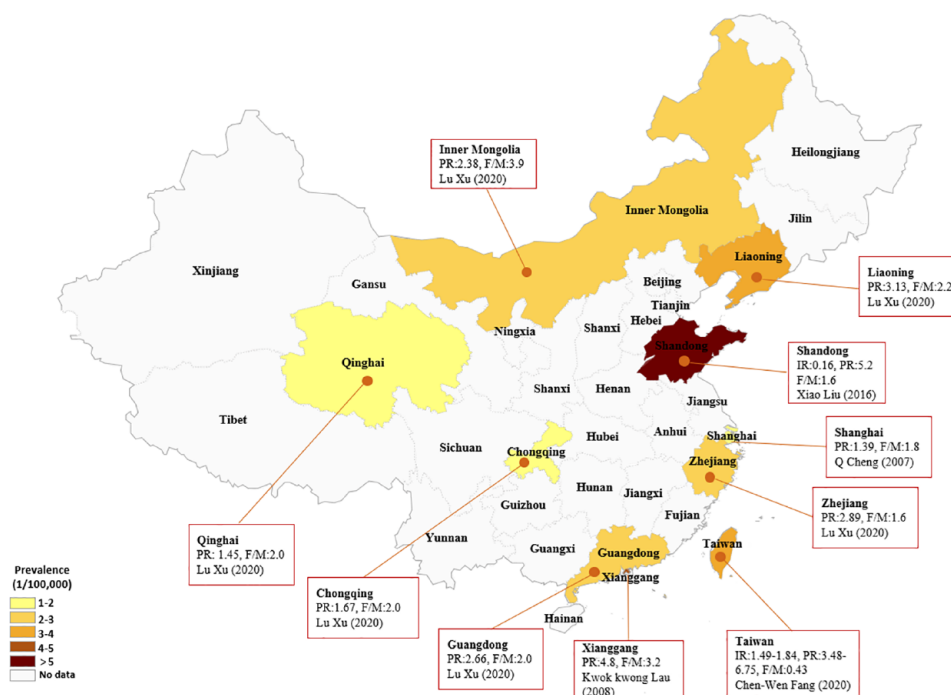
Figure 1. The epidemiological characteristics of MS in different regions of China.
MS, multiple sclerosis.

such as Malaysia and Thailand, the gender difference was more significant (5:1 and 6.2:1, respectively).[119,120] In this review, the F/M ratio was estimated to be 2.0 in China, after reviewing all data from 92 studies related to MS (Table 1). This result was similar to that reported in Italy and Kuwait.[121,122]

China is divided into Northern and Southern parts by the Huai River and Qinling Mountains. We compared the numbers of female and male patients as well as the F/M ratio in Northern China with their counterparts in Southern China. As shown in Table 2, the total number of patients, as well as the number of female and male patients in the north, was significantly higher than that in the south. The data followed the laws of geographical distribution. As we know, geographical location plays an important role in the development of MS.[123] Both in Southern and Northern China, we found significantly more female MS patients than male patients. However, there was no significant correlation between sex ratio with latitude (1.79 in Northern China *versus* 1.82 in Southern China) (Table 2), consistent with previous reports.[124]

MS mainly starts affecting patients at an age of 20–40 years.[3,125–127] The highest prevalence rates

of pediatric multiple sclerosis is aged 13–16.[127] Up to 10% of MS patients present demyelinating before 18 years.[128] In China, the average age of MS often occurred in adults aged around 41.53 years and children aged around 8.05 years (Table 1).

Clinical features
Clinically isolated syndrome (CIS) is the occurrence of the initial demyelinating event with a high suspicion of development of MS.[129] Due to the lack of specific biomarkers, the diagnosis of MS is established in the fulfillment of dissemination in space (DIS) and time (DIT) demonstrated by the combination of clinical manifestations, imaging and cerebrospinal fluid (CSF) analysis [especially oligoclonal bands (OCBs)].[130] The development of McDonald's criteria for MS and gradual improvement over time makes the diagnosis of MS more accurate and may allow the earlier diagnosis and treatment.

MS subtypes and course
According to the clinical course, several different phenotypes of MS have been defined: relapsing-remitting MS (RRMS), secondary

Table 2. Clinical features of patients with MS between geographical regions in China.

MS features	Northern China	Southern China	References
Demographics			
F/M ratio	4495/2513 (1.79)	1991/1096 (1.82)	Cui *et al.*,[11] Ren and Qiao,[12] Guo *et al.*,[13] Cheng and Li,[14] Wang,[15] Fan *et al.*,[16] Long *et al.*,[17] Liu and Feng,[18] Qian,[19] Li *et al.*,[20] Wang,[21] Han and Liu,[22] Zheng,[23] Wang *et al.*,[24] Wang,[25] Cheng *et al.*,[26] Ren *et al.*,[27] Li *et al.*,[28] Zhu *et al.*,[29] Duan,[30] Gong,[31] Jia,[32] Wang and Wei,[33] Chen,[34] Duan and Hua,[35] Kong,[36] Zhang,[37] He and Zou,[38] Liu and Huang,[39] Li and Zhou,[40] Qiu,[41] Lin *et al.*,[42] Song,[43] Lin *et al.*,[44] Zhao *et al.*,[45] Xu,[46] Liu *et al.*,[47] Zhu *et al.*,[48] Ma and Liu,[49] Xue,[50] Xie *et al.*,[51] Chen *et al.*,[52] Hu and Chang,[53] Yang and Yang,[54] Lu *et al.*,[55] Zhang,[56] Liu *et al.*,[57] Zhao *et al.*,[58] Zhang *et al.*,[59] Huang and Chen,[60] Su,[61] Hu,[62] Ruan,[63] Zeng *et al.*,[64] Wang *et al.*,[65] Chen *et al.*,[66] Meng,[67] Zhou and He,[68] Wu,[69] Zhou and Luo,[70] Zhang *et al.*,[71] He *et al.*,[72] Lv,[73] Li,[74] Bai,[75] Yin,[76] Zhou and Fu,[77] Ouyang and Zhu,[78] Huang *et al.*,[79] Lin,[80] Xing *et al.*,[81] Shi,[82] Wang,[83] Feng,[84] Han,[85] Chan *et al.*,[86] Liu *et al.*,[87] Chan *et al.*,[88] Long *et al.*,[89] Yang *et al.*,[90] Li *et al.*,[91] Liu *et al.*,[92] Chen *et al.*,[93] Liu *et al.*,[94] Zhang *et al.*,[95] Lu *et al.*,[96] Fang *et al.*,[97] Zhang *et al.*,[98] Zhao *et al.*,[99] Zheng *et al.*,[100] Xu *et al.*,[101] Zhao *et al.*,[102] Lai *et al.*[103]
Clinical manifestations			Cui *et al.*,[11] Long *et al.*,[17] Wang,[21] Zheng,[23] Zhu *et al.*,[29] Gong,[31] Wang and Wei,[33] Duan and Hua,[35] He and Zou,[38] Qiu,[41] Zhao *et al.*,[45] Hu and Chang,[53] Yang and Yang,[54] Su,[61] Zeng *et al.*,[64] Meng,[67] Yin,[76] Huang *et al.*,[79] Lin,[80]
Optic neuritis (%)	401/2021 (19.8)	442/1913 (23.1)	
Limb weakness (%)	772/2021 (38.2)	694/1913 (36.3)	
Sensory disturbances (%)	707/2021 (35.0)	493/1913 (25.8)	
Sphincter dysfunction (%)	133/2021 (6.7)	85/1913 (4.4)	
Ataxia (%)	146/2021 (7.2)	143/1913 (7.5)	
Cognitive impairment (%)	25/2021 (1.2)	47/1913 (2.5)	
Epilepsy (%)	12/2021 (0.6)	21/1913 (1.0)	
Consciousness disturbance (%)	23/2021 (1.1)	28/1913 (1.4)	
Cranial nerve involvement (%)	241/2021 (12.4)	109/1913 (5.7)	
CSF study			Cui *et al.*,[11] Wang,[15] Liu and Feng,[18] Zheng,[23] Wang,[25] Zhu *et al.*,[29] Duan,[30] Zhao *et al.*,[45] Zhu *et al.*,[48] Ma and Liu,[49] Hu and Chang,[53] Yang and Yang,[54] Su,[61] Zhou and Luo,[70] Bai,[75] Ouyang and Zhu,[78] Huang *et al.*,[79] Lin,[80] Feng,[84] Long *et al.*[89]
White cell count (>8 cells/mm^3) (%)	101/457 (22.1)	159/620 (25.6)	
Protein (>0.25 g/L)	162/598 (27.1)	170/703 (24.5)	

(Continued)

Table 2. (Continued)

MS features	Northern China	Southern China	References
IgG index >0.7 (%)	113/255 (44.3)	80/201 (39.8)	
OCB (%)	169/476 (35.5)	502/904 (55.5)	
MRI features			
Brain MRI abnormalities (%)			Cui et al.,[11] Guo et al.,[13] Wang,[15] Li et al.,[20] Ren et al.,[27] Li et al.,[28] Zhu et al.,[29] Duan,[30] Gong,[31] Jia,[32] Wang and Wei,[33] Lin et al.,[42] Lin et al.,[44] Xu,[46] Zhu et al.,[48] Hu and Chang,[53] Huang and Chen,[60] Hu,[62] Ruan,[63] Bai,[75] Yin,[76] Zhou and Fu,[77] Ouyang and Zhu,[78] Long et al.,[89] Zhao et al.[99]
Periventricular lesions	432/768 (56.3)	629/867 (59.1)	
Cortical lesions	302/768 (39.3)	499/867 (57.5)	
Cerebellar lesions	123/768 (16.0)	74/867 (8.5)	
Brainstem lesions	302/768 (39.3)	240/867 (27.7)	
Spinal cord MRI abnormalities (%)			Cui et al.,[11] Guo et al.,[13] Qian,[19] Li et al.,[20] Zheng,[23] Duan,[30] Duan and Hua,[35] Liu et al.,[47] Xue,[50] Su,[61] Hu,[62] Ruan,[63] Meng,[67] He et al.,[72] Ouyang and Zhu,[78] Huang et al.,[79] Lin,[80] Feng,[84] Han,[85] Yang et al.,[90] Liu et al.[92]
Cervical cord lesions	285/670 (42.5)	135/597 (22.6)	
Thoracic cord lesions	135/670 (20.1)	109/597 (18.3)	
Cervical and thoracic cord lesions	54/670 (8.0)	39/597 (6.5)	
Lumbar cord lesions	11/670 (1.6)	8/597 (1.3)	

Data are presented as *n* (%).
CSF, cerebrospinal fluid; IgG, immunoglobulin G; MRI, magnetic resonance imaging; MS, multiple sclerosis; OCB, oligoclonal bands.

progressive multiple sclerosis (SPMS), and primary progressive MS (PPMS).

Almost 80–85% MS patients belong to RRMS.[131] A study showed that almost 50% of RRMS patients could develop SPMS within 15 years.[132] Of the 92 articles retrieved, only 30 articles reported relevant data (Table 1). According to the current data, RRMS is the most common phenotype in China and accounts for 85.2% of all MS patients, which is similar to the data from other regions, such as Argentina[133] and Lebanon.[134] Other phenotypes are SPMS and PPMS, with the percentage of 8.6% and 6.2%, respectively. In a 3-year follow-up study about CIS carried out in 2011 in China, 25.0% of patients finally converted to clinically definite MS (CDMS), with a higher conversion rate in females than males. Patients who had multifocal lesions had a greater likelihood of converting CDMS.[87] In a study including 249 patients with MS in 2008 in Shanghai, the proportion of RRMS, SPMS, and PPMS was 86.3%, 6.4%, and 1.6%, respectively. The remaining patients were hard to classify.[135] A two-center study conducted in 2019 reported that there were 115 patients (81.0%)

with RRMS, 21 patients (15.0%) with PPMS, and 6 patients (4.0%) with SPMS.[96] In a prospective study in China including 365 patients followed up until reaching the expanded disability status scale of 6.0, 34 (9.3%) RRMS patients developed into the stage of SPMS, with a bit predominance in males (male:female = 10.9:8.5).[98]

Clinical manifestations

The clinical features of an MS attack are various, depending on the regions of CNS targeted. The most common clinical phenotypes are optic neuritis (ON), transverse myelitis (TM), brainstem, and cerebellar syndromes. However, there exist other less common clinical manifestations related to cortical lesions, such as seizures and aphasia.[126]

Optic neuritis. ON is a common initial presentation characterized by the subacute and unilateral attack with a gradual worsening of vision and photophobia, etc.[136–138] In 2013, a study reported that ON was the second most symptom in Latin American MS patients,[139] which was similar to the results from the cohort of Polish MS patients.[140] A study from Egypt showed that visual symptoms (21%) and motor dysfunction (21%) were the most common presenting features, and females were more prone to develop visual damage than males.[141] However, we observed that ON was the third clinical presenting complaint in China (Table 1), which was consistent with the data in Mexico presented by Bertado-Cortés *et al.*[142] In addition, in a study of 184 MS patients in South China, the results showed that there was no difference in the incidence of ON between OCB-positive and OCB-negative MS patients,[96] which was agreement with studies from other European countries, such as Serbia[143] and Greece.[144] A comparative study from Turkey demonstrated that there was no difference between OCB (+) and OCB (−) patients with respect to visual evoked potentials abnormalities.[145] And another Chinese study showed OCB had no effect on the final outcome of vision.[146]

Transverse myelitis. Spinal cord involvement is the most common clinical manifestations of MS.[147] Compared to other continents, the advantage of the frequency of TM over that of visual disorders in Asia seems to be no significant.[142,148–151] A study comparing clinical characteristics between the Middle East and North Africa patients and Indian patients *versus* patients with European descent showed the frequency of spinal cord symptoms was not different between these groups.[151] A survey enrolled 142 MS patients in Pakistan showed that the most common initial symptoms were motor weakness (70%), followed by sensory symptoms (45%), while only 15% had bladder dysfunction.[152] Kim *et al.*[153] also reported the low frequency of bladder/bowel dysfunction (9%) in Korea. However, in Indian, the most frequent initial presentation was motor weakness in almost 85.1% of MS patients. Sensory symptoms and bladder dysfunction were present in 41.6% and 65.1% of patients, respectively.[154] In a multicenter study from Brazil, the frequency of urinary system symptoms was 50%,[155] which was higher than the reported from a Chinese study, with the proportion of 3.3%.[92] We found that limb weakness was the most common complaint and occurred in 42.5% of MS patients in China. Sensory disturbances and sphincter dysfunction occurred in 35.8% and 9.5% of the patients, respectively (Table 1).

Brainstem symptoms. Brainstem involvement in MS can cause ocular motility disorder such as diplopia and nystagmus, especially diplopia.[156] Internuclear ophthalmoplegia is a common acute ocular motor manifestation in MS, which can occur in approximately 33% of patients.[157] Brainstem involvement was reported in a study of 14,969 cases with MS at a proportion of 19.6%.[158] A single-center retrospective study in a cohort of 375 Polish MS patients reported that 9.3% of patients presented with diplopia, 5.9% with cranial nerves dysfunction.[140] One study from Northern China showed that 24.8% of MS had nystagmus, 6.8% had diplopia, and 10.3% had dysarthria.[91] Generally, the cranial nerve involvement occurred in 12.5% of MS patients in China, mainly eye movement-related nerves (10.6%), followed by bulbar weakness (1.1%) and facial palsy (0.6%) (Table 1). Other less common symptoms included vertigo, trigeminal neuralgia, and vomiting. In addition, the frequency of cranial nerves dysfunction in Northern China was slightly higher than that in Southern China (12.4% and 5.7%, respectively) (Table 2). Both of them were mainly with ocular motility disorder.

Cerebellar symptoms. The injury of the cerebellum and its related pathways are also common in MS, especially in advanced disease states. Wilkins

reported that the prevalence of cerebellar ataxia could be up to 80% in MS patients.[159] Tremor may affect limbs, head, and trunk. Postural or intention tremor is the most common type.[160] Severe tremor tends to be suggestive of poor prognosis. At the early stage of MS, the presence of cerebellar signs and symptoms tends to indicate the early occurrence of higher disability.[161] In a study of 221 patients with early-onset MS,[162] as one of the initial presentations, cerebellar signs occurred in 14.6% of all patients, which was consistent with the result reported by Kalincik *et al.*[158] that the cerebellar symptoms occurred in 10.1% of patients. Another previous study reported that tremor may occurred in up to 25−60% of MS patients.[163] Interestingly, a study from Saudi Arabia[164] showed that there was no difference of the frequency of cerebellar symptoms between males and females, while the result was distinct from other studies from Mexico[142] and Egypt.[141] They stated ataxia and tremors were more common in males than in females. We found that the frequency of ataxia in China was 14.1% (Table 1), which was comparable to the study from Jordan.[165] Patients from Northern China tend to have higher proportion of ataxia than patients from Southern China (7.2% *versus* 7.5%, respectively) (Table 2).

Cognitive impairment. Due to continuous axonal loss and atrophy of white matter and gray matter, MS patients have cognitive impairment (CI). The prevalence of CI in MS ranges from 40% to 65%[166] occurring in all MS phenotypes. However, it is more frequent and severe in progressive MS than in RRMS, which suggests that cognitive deficits tend to aggravate due to the exhaustion of nervous system reserve over time.[167] Some studies from European countries[168–170] and Latin America[171] reported the prevalence of CI was between 34% and 65%. Generally, the older patients are likely to have worse cognitive performances than young patients, while CI is mostly directly related to MS itself and not similar to the decline in CI with general aging.[172,173] However, we found that only 4.2% of Chinese patients presented with CI (Table 1), which was very lower than the result from other Asia countries, such as Kuwait (23.3%)[174] and Korea (50%).[175] While a study with only very early MS patients showed the prevalence of CI was 11.6%.[176] We speculate that the low frequency of CI may be related to the stage of disease and selected testing methods and scales. In the early stage, these symptoms may be obscure and easily neglected.

Other symptoms. There are several other less common clinical syndromes, such as epilepsy and consciousness disturbance. Epilepsy is rare in MS and related to cortical or subcortical demyelinating lesions and atrophy of cortex and gray matter.[177] We found that epilepsy occurred in 0.7% of MS patients in China, smaller than that in Iran and Germany (2.3% and 2.6%, respectively).[178,179] Consciousness disturbance was also uncommon in Chinese patients with the prevalence of 1.0% (Table 1).

Comorbidity

Recently, many studies focus on the field of in MS.[180,181] Comorbidity is one of the clinical characteristics in MS patients and seems to be related to disability. Comorbidities of MS can be divided into two categories: autoimmune and nonautoimmune comorbidities.

Increasing evidence has shown that autoimmune comorbidities are prevalently presented in MS and associated with the disease progression. The frequency of autoimmune comorbidity ranged from 0% to 7.74%. The most prevalent autoimmune and neurological autoimmune comorbidities were psoriasis, thyroid disease, and myasthenia gravis (MG).[182,183] Danish reported that there was a significantly higher proportion with autoimmune diseases, including diabetes mellitus type I, Crohn's disease, and systemic lupus erythematosus (SLE) in male patients with MS, than non-MS male controls. In this study, Crohn's disease and ulcerative colitis were the most frequent autoimmune comorbidities in MS patients.[184] Another study comprising 2725 patients from Serbia demonstrated the prevalence of autoimmune disorders was 6.06% and the thyroid disease was the most common autoimmune disease.[185] However, we found that Sjogren syndrome and MG were the most common systemic and neurological autoimmune diseases, respectively, in China (Table 1), which was in consonance with the result from another Chinese study.[97]

In addition to the autoimmune diseases, there is also a high prevalence of nonautoimmune diseases in MS. Hypertension, chronic lung disease,

and hyperlipidemia are the most common nonautoimmune comorbidities.[186] Studies have suggested that these comorbidities are associated with the clinical course of the disease, disability progression, and higher increased mortality.[187,188] Increased risk of certain comorbidities may be the consequence of immunotherapy in MS patients.[185] In a Chinese study cohort, cardiovascular diseases, especially hypertension were the most common nonautoimmune diseases in MS patients.[189] Other studies from European and American countries also confirmed this point.[190–192] However, aging is largely correlated with the increased frequency of these comorbidities in MS patients.[193]

Characteristics of CSF

Since the high heterogeneity of clinical manifestations, the diagnosis of MS is complex depending on the comprehensive consideration of clinical presentations, imaging, and laboratory findings. In most patients with MS, CSF can still provide valuable evidence.

We analyzed all data collected and found that a total of 24.1% of MS patients in China showed mildly raised white cell count. The frequency of raised protein was 25.5%, mainly in the range of 0.4–0.9 g/L (Table 1), and similar to the previously reported findings from China and other countries.[134,135,194] In addition, there seems to be no significant difference in the proportion of raised white cell count and protein between Northern with Southern China (Table 2).

Although only 70% of all MS patients exhibited elevated immunoglobulin G (IgG) index, it can take the integrity of the blood–brain barrier into consideration and is regarded as the valuable diagnostic hallmark in MS.[195] Olsson and Pettersson[196] found that the frequency of elevated IgG index in MS patients was higher than that in patients with other neurological diseases. However, in a previous study, IgG index >0.7 was observed in only 46.2% of patients,[197] while another study in Korea showed that this proportion was 60%. Interestingly, a study of Czech Republic displayed different IgG index in different types of MS, with 49.3% in CIS, 69.8% in RRMS, 63.5% in SPMS, and 66.6% in PPMS.[198] We found that the frequency of raised IgG index was 20.4% in China (Table 1). The frequency of elevated IgG index in Northern China was higher than that in Southern China (44.3% *versus* 39.8%, respectively) (Table 2).

Excessive intrathecal synthesis of IgG is also confirmed by detecting OCBs. Almost 95% of MS patients have OCBs in CSF in Sweden.[199] However, only 48.6% OCBs positive occurred in MS patients of China (Table 1), which was a little lower than that in other Asian countries, with 62% in Japan,[200] 53% in Korea,[153] and slightly higher than 44.2% in Jordan,[165] but lower than that in Western countries.[201–203] When compared with Northern China, OCBs positive occurred more frequently in Southern China (35.5% *versus* 55.5%, respectively) (Table 2). Another study in China showed that patients with early-onset age tended to have OCBs in CSF than elder patients, while there was no association between OCBs status and the clinical findings.[96] Liu *et al.*[87] also observed a high conversion rate to CDMS in OCB-positive patients compared to OCB-negative patients although without obvious statistical significance. However, Kolčava *et al.*[129] demonstrated that during a follow-up lasting a mean of 27 months, OCB positivity was a strong predictor for the conversion of CIS to MS. Interestingly, the OCB positivity was correlated with latitude, that is, the probability of being OCB positive may increase with enhancing distance from the equator.[204,205] But the study from Argentina showed latitude seemingly regardless of OCB prevalence.[206] This relationship should be investigated in more countries and larger patients.

Imaging features

Magnetic resonance imaging (MRI) is increasingly used to find the evidence that is suggestive of MS diagnosis, especially for patients with OCB and other tests negative results, and monitor its progression. As showed in standard MRI, the Dawson fingers of the periventricular lesions, ovoid lesions within characteristic locations, juxtacortical and infratentorial, and corpus callosum lesions are suggested as typical brain MRI findings, while short lesions (usually no more than three vertebral segments) with a clear boundary and mild edema, mainly involving the dorsolateral cord as specific spinal cord MRI findings. For most patients, the McDonald diagnostic criteria require demonstration of DIS and DIT with MRI findings. Given the relative low specificity and poor correlation with disability measures of

conventional imaging, some specific MRI features, such as the central vein sign (CVS) and iron deposition, may provide new insight into the pathophysiology of MS and increase the specificity of MS diagnosis.

Brain

Periventricular lesion. Periventricular region seems to be more likely to subjected to demyelination.[207] In 2020, a study evaluated lesions distribution to distinguish between NMOSD, MS, and myelin oligodendrocyte glycoprotein antibody-associated disorders. They found that 61 (61/71, 85.9%) of 71 MS patients have periventricular lesions. In another study, almost 96.0% of RRMS patients had specific periventricular lesions. However, periventricular lesions were observed in only 64.9% of MS patients in China (Table 1).[93,208] The low frequency of periventricular lesions is largely related to the MRI technique, since MS patients are mostly received MRI examination with two-dimensional (2D) imaging in many Chinese regions. There was also no difference in the distribution of periventricular lesions between MS patients with and without OCBs,[99] while an opposite result in Japan indicated that periventricular lesions were correlated with OCB state.[209]

Juxtacortical or cortical lesions. The juxtacortical or cortical lesion is a characteristic of MS and can be detected in almost 78% of MS patients and 20–72% of CIS patients.[210–213] In CIS patients, ⩾1 cortical lesion can increase the specificity to identify those who have the potential to convert to MS.[214] Moreover, the MRI evidence of cortical lesions is predictive for SPMS conversion. Patients with large cortical lesion counts have a high probability to develop SPMS.[215,216] Interestingly, it was found that male patients had more possibility to develop cortical lesions than females.[217] We found that cortical lesions were detected in 38.7% of MS patients (Table 1), which was higher than a study from Qatar[218] and another Chinese study,[93] but lower than Zhao *et al.*[99] reported.

Infratentorial lesions. Infratentorial lesions is one of the characteristic damage locations in MS. Favored targets of MS lesions are the brainstem and cerebellar peduncles, mainly brachium pontis.[219] Infratentorial lesions are more sensitive and specific for MS diagnosis than periventricular lesions.[208,220]

The involvement of brainstem in MS is very common. Up to 58.0% of patients with MS can be detected with brainstem lesions.[221] Among three anatomic sites, the pons is more frequently involved. However, only 33.1% of Chinese patients had brainstem lesions (Table 1), which was lower than that in many Western countries.[222–225] The distribution of MRI lesions in the brainstem was 11.5% in the midbrain, 26.3% in the pons, and 12.9% in the medulla (Table 1). Although MRI lesions found in Japan were higher than our results, it was still lower than in Western countries.[226] It is speculated that the ethnic factors may play an important role resulting in the difference. Of course, MRI's program with different spatial resolutions can also contribute to this result.[227] Besides, CIS patients both with symptomatic and asymptomatic brainstem lesions are more likely to develop MS than patients only with symptomatic brainstem lesions.[228]

Cerebellar injury is also common in MS, which is the origin of many manifestations. Lesions can affect any part of the cerebellum.[229] Similar to the brainstem, there is a difference in the percentage of cerebellar involvement between different countries. In China, 12.0% of MS patients had cerebellum lesions (Table 1). We shared a similar result with a study in Japan,[226] but the percentage was low significantly compared to white patients with MS.[230,231] This relationship needs to be confirmed by future studies.

Spinal cord. The typical spinal cord MRI findings in MS patients are featured with T1-hypointense and T2-hyperintensity.[232,233] Gadolinium-enhancing lesions in the spinal cord are less seen than in the brain and are usually accompanied by new clinical symptoms.

Types of spinal cord lesions vary depending on the MS subtype. As mentioned before, asymptomatic spinal cord lesions have been proposed in 30–40% of CIS patients. Focal lesions are more seen in RRMS patients.[229] When RRMS patients progress to a secondary progressive course or patients start with a primary progressive course, spinal cord abnormalities tend to be diffuse and extensive, which is often correlated with spinal cord atrophy.[229,234] Abnormal spinal cord imaging was seen in 61.4% of MS patients in China (Table 1), which was lower than previously reported,[235,236] but similar to a previous study in

China reported with a frequency of 63%.[92] What is more, two Chinese studies have shown that there was no difference in the number of spinal cord lesions between OCB-positive and OCB-negative patients.[96,99] While postmortem studies demonstrated that demyelination affects the entire spinal cord,[237,238] MRI detection of such lesions is regularly more successful in the cervical proportion.[234,239–242] In our study, among patients who had spinal cord abnormalities, cervical cord lesions were found in 33.1% of cases, thoracic cord in 17.7%, and 1.5% in lumbar cord. 7.3% of patients had both cervical and thoracic cord lesions (Table 1). However, there was a higher ratio of thoracic cord involvement than cervical cord in Korean.[243] In a study of 202 patients with MS, cervical cord abnormalities were seen in 59% of patients; the percentage was higher than that of involved thoracic or lumbar cord.[241] Andreadou *et al*.[144] showed that OCB-positive patients had the higher frequency of cervical spinal cord lesions than OCB-negative patients. Nevertheless, the number of cervical spinal cord lesions did not differ by OCB status in Turkey.[145] Asian-type MS tends to have higher frequencies of spinal cord lesions as well as gadolinium-enhanced lesions than Western-type MS.[244]

Specific MRI features as biomarkers

Central vein sign. CVS is regarded as a kind of phenomenon of the MRI-detectable perivenular distribution of demyelinating lesions.[245] As a newly proposed biomarker of inflammatory demyelination, the CVS is increasingly recommended for improving the accuracy of MS diagnosis.[246] A number of groups have evaluated the CVS in various conditions, including Susac's syndrome, NMOSD, and inflammatory vasculopathies, and increasing evidence has demonstrated CVS as a potential imaging marker to accurately distinguish MS from non-MS mimics.[247–250] Studies have identified that the CVS could be present in all subtypes of MS, and there was no difference between clinical phenotypes regarding the proportion of total lesions with a central vein.[251,252] In terms of the distribution, the CVS has a predilection for the periventricular region, which was consistent across studies.[253,254] However, large prospective studies are still needed to validate the clinical value of CVS as a novel indicator to support the diagnosis of MS. As in other middle- and low-income countries, so far, MRI examination with 2D imaging has been applying in

China; therefore, the CVS as an important imaging marker could not be identified well, which is needed to be improved as soon as possible.

Iron deposition. Iron is an essential element that functions in normal neurobiological processes, including neurotransmitter synthesis and myelin production.[255] In the aging process, iron can accumulate in brain tissue. However, it has demonstrated that abnormal deposition of iron in the brain may be related to neurodegeneration.[256] MRI has been proposed as a powerful mean for quantifying iron deposition in brain lesions and typically exhibits a rim of hypointense signal fully or partially encircling lesions, the so-called iron rims (IRs).[257] IRs can be detected by several MRI techniques, such as conventional T2-weighted MRI, susceptibility weighted imaging, and quantitative susceptibility mapping.[258] Histopathological-imaging studies identified that, IRs in MS lesions are predominantly from activated microglia and macrophages and considered to represent chronic active lesions.[259] IRs can be detected in different MS subtypes. Llufriu *et al*.[260] found the detectable frequency of IRs in SPMS patients is higher than in RRMS patients, which is similar to the finding by Chawla *et al*.,[250] but different from another study.[261] Importantly, age and sex differences may influence the occurrence of IRs in MS patients. IRLs are more common in young male MS patients,[251,262] and IRs may be also useful biomarkers for improving the accuracy of MS diagnosis. Many studies found that IRs are rare in non-MS inflammatory neurological diseases, including NMOSD,[263] Susac syndrome,[264] SLE, and other inflammatory demyelinating diseases of CNS.[265,266] Besides, IRs are also better markers for evaluating neurological disability and more brain atrophy.[267,268]

Treatments

Management of MS requires to be integrated multidisciplinary approach and immunomodulating treatments. Many clinically conventional and novel medications with distinct targets have been approved for immunomodulatory and immunosuppressive treatments. In the acute phase, patients can be treated with corticosteroids to inhibit inflammatory and autoimmune activity. During the remission and relapse phases, all kinds of DMTs, especially several novel monoclonal antibodies (Mab), targeting different targets

modify the process of MS reducing relapse by inhibiting or regulating immune response.[269]

Treatment of acute relapses

The aim of acute relapse treatment is to accelerate clinical recovery without effect on long-term prognosis. However, the relapse severity decides the need for acute treatment in MS. The standard treatment for MS relapses is the intravenous infusion of high-dose corticosteroids in a short time.[270] If the initial response to steroids is inadequate, rescue treatment is available, including plasma exchange or intravenous immunoglobulin.[271]

According to the Chinese expert consensus on MS diagnosis and treatment, the recommend first-line therapy in the acute phase is glucocorticoids. If the clinical neurological deficit recovered obviously, it can be stopped directly. The second-line therapy is plasma exchange.[272] A study explored the factors associated with the efficacy of glucocorticoid in Chinese patients with MS.[273] The results showed that patients who were sensitive to glucocorticoid had higher expression of glucocorticoid receptor (GR)-α and lower expression of FK506 binding protein 5 (FKBP5), which might provide a novel therapeutic strategy for glucocorticoid-resistant patients with MS in the acute stage.

Treatment of remission

Conventional immunosuppressants. Since the introduction of interferon-β (IFN-β) into the Chinese medical market, people certainly start to be exposed to the concept of 'DMTs'. However, before that, the lack of potent drugs for MS always makes patients as well as doctors helpless. Thus, Chinese doctors have no choice but to choose medicine best for patients among conventional immunosuppressants, which have been demonstrated to be effective in MS, such as azathioprine and mycophenolate mofetil. Despite adverse effects, they are widely used in MS patients in China due to the low price and confirmed effectiveness.[274] A clinical trial for MS in Italy showed that azathioprine could function in reducing new brain inflammatory lesions.[275,276] A prospective double-masked trial enrolled 59 American MS patients displayed that treatment with azathioprine could significantly decline the risk of disability and relapse, leading to the delay of MS progress.[277] However, there is some

concern about its safety, mainly a possible increased risk of malignancy. But cumulative doses of 600 g seem to decline the incidence of side effects.[278] A retrospective study also confirmed the effect of mycophenolate mofetil on MS. This study enrolled 344 MS patients (median follow-up 25.3 ± 1.1 months), and the result showed that during the 1-year control period, the recurrence rate significantly decreased and kept the disability at the initial level.[279]

Disease-modifying therapies. Over the last few years, the treatment of MS has experienced a revolution since the advent of more potent DMT drugs. All of these medicines have been identified to be effective in decreasing the frequency of relapses and accumulation of lesions, thereby slowing disease progression. Up to now, since the invention of the first immunomodulating IFN-β-1b in 1993, 15 DMTs have been currently approved in various regions worldwide for modifying the course of MS. To date, there have been only four licensed DMTs available in China: IFN-β, teriflunomide, fingolimod, and siponimod. A recent study on the survival analysis of MS patients showed that financial burden, symptom degree, and educational level all govern the treatment acceptance in Chinese patients with MS.[269]

IFN-β was added to the National Medical Insurance Drug List in 2017 in China. As a first-line treatment for MS, IFN-β can reduce the relapse rate, disability, and MRI prognostic indicators.[280] Unfortunately, it has been excluded from National Medical Insurance Drug List. Due to the expensive cost and intolerance of injection administration, IFN-β is becoming less and less unaccepted by Chinese MS patients.

Teriflunomide, as the first orally DMTs approved in China, can suppress the proliferation of activated lymphocytes by inhibiting of the dihydroorotate dehydrogenase, hence reducing CNS lymphocyte infiltration.[281] The Phase III TOWER study of teriflunomide in China has been completed and showed the marked extent of efficacy and excellent safety in Chinese subjects.[282] Meanwhile, compared with IFN-β, teriflunomide is more cost-effective.[283]

With the increasing diagnostic rate of SPMS in China, the use of sphingosine 1-phosphate (S1P)-receptor modulators fingolimod and siponimod are increasing gradually. However, there is a lack

of data related to the efficacy and safety of the S1P receptor modulators for MS in China because phase III clinical trials are still going now.

Recently, several new Mabs as DMTs have started to treat MS patients in China, such as anti-CD20 Mabs's rituximab and ofatumumab, which are highly precise by specifically targeting molecules displayed on cells involved in distinct immune mechanisms of MS pathophysiology. So far, the efficacy and safety of Mabs in Chinese MS patients have not been reported.

Furthermore, transplantations of umbilical cord mesenchymal stem cells and autologous mesenchymal stem cell in MS were conducted in China and other countries, which requires further study to confirm its effectiveness and safety.[81,284]

Prospect and challenges

The clinical research is gradually enriching our knowledge of MS; however, it remains a complex and challenging condition. The epidemiology, clinical features, and therapy of MS differ within distinct countries in the globe and Chinese different regions. In this review, we provide the overall profile of MS in China and global research advance on MS, which can help us to recognize risk factors, signs, and symptoms suggestive of MS in order to make early diagnosis, and appropriate and timely treatment. Although most kinds of existing DMTs can prevent relapse, hinder focal brain inflammation, and partly slow long-term progression, they are mainly available to RRMS patients and a minority of people with progressive forms of the disease. Therefore, an important topic for future studies would be to elucidate the mechanisms of neurodegeneration and explore available biomarkers to diagnose and monitor disease progression and, thus, to drive the development of new treatment combining neuroprotection with remyelination to promote lesion repair and prevent progressive accumulation of disability. However, there are some deficiencies and problems in China and other low- and middle-income countries in this regard as described above, which leads to misdiagnosis and delayed timely treatment. These challenges need national and international cooperation to solve in the future.

Declarations

Author contributions
Meng Wang: Conceptualization; Data curation; Formal analysis; Investigation; Methodology; Software; Writing – original draft.

Caiyun Liu: Data curation; Formal analysis; Resources; Writing – review & editing.

Meijuan Zou: Data curation; Formal analysis; Resources; Writing – original draft.

Zixuan Niu: Data curation; Formal analysis; Resources; Writing – original draft.

Jie Zhu: Conceptualization; Methodology; Project administration; Supervision; Writing – review & editing.

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References
1. Brundin L, Kobelt G, Berg J, *et al.*; European Multiple Sclerosis Platform. New insights into the burden and costs of multiple sclerosis in Europe: results for Sweden. *Mult Scler* 2017; 23: 179–191.

2. Eskandarieh S, Heydarpour P, Minagar A, *et al.* Multiple sclerosis epidemiology in East Asia, South East Asia and South Asia: a systematic review. *Neuroepidemiology* 2016; 46: 209–221.

3. Heydarpour P, Khoshkish S, Abtahi S, *et al.* Multiple sclerosis epidemiology in Middle East and North Africa: a systematic review and meta-analysis. *Neuroepidemiology* 2015; 44: 232–244.

4. GBD 2016 Neurology Collaborators. Global, regional, and national burden of neurological disorders, 1990–2016: a systematic analysis for the Global Burden of Disease Study 2016. *Lancet Neurol* 2019; 18: 459–480.

5. Howard J, Trevick S and Younger DS. Epidemiology of multiple sclerosis. *Neurol Clin* 2016; 34: 919–939.

6. The Multiple Sclerosis International Federation. Atlas of MS. 3rd ed, https://www.atlasofms.org (2020).

7. Baecher-Allan C, Kaskow BJ and Weiner HL. Multiple sclerosis: mechanisms and immunotherapy. *Neuron* 2018; 97: 742–768.

8. Wekerle H. B cells in multiple sclerosis. *Autoimmunity* 2017; 50: 57–60.

9. Sabatino JJ Jr, Zamvil SS and Hauser SL. B-cell therapies in multiple sclerosis. *Cold Spring Harb Perspect Med* 2019; 9: a032037.

10. Gelfand JM, Cree BAC and Hauser SL. Ocrelizumab and other CD20(+) B-cell-depleting therapies in multiple sclerosis. *Neurotherapeutics* 2017; 14: 835–841.

11. Cui C, Lou J and Yang X. Clinical characteristics and treatment analysis of 105 cases of multiple sclerosis. *Chin J Pract Nerv Dis* 2011; 14: 10–12.

12. Ren H and Qiao H. Clinical retrospective analysis of 16 cases of multiple sclerosis. *Chin J Pract Nerv Dis* 2012; 15: 66.

13. Guo M, Xu J and Jia Y. Clinical analysis of 200 cases of multiple sclerosis. *Chin J Neuroimmunol Neurol* 2013; 20: 366–367.

14. Cheng Z and Li H. Clinical analysis of 20 cases of multiple sclerosis. *Chin J Pract Nerv Dis* 2011; 14: 52–53.

15. Wang L. *Clinical analysis of 24 patients with pediatric multiple sclerosis*. Chongqing Medical University, https://d.wanfangdata.com.cn/thesis/D01453654 (2018).

16. Fan Y, You Y and Chen K. Clinical characteristics and distribution of TCM syndromes in 261 patients with multiple sclerosis. *J Capital Med Univ* 2012; 33: 301–306.

17. Long G, Su J and Tang J. Magnetic resonance imaging of 31 patients with multiple sclerosis. *J Diagn Concepts Pract* 2014; 13: 602–605.

18. Liu G and Feng T. Clinical analysis of 36 cases of multiple sclerosis. *Chin J Pract Nerv Dis* 2013; 16: 80–81.

19. Qian N. Clinical analysis of MRI manifestations of 40 cases of multiple sclerosis. *China Pract Med* 2014; 9: 92–93.

20. Li L, Yang Z and Wang H. Clinical analysis of 52 cases of multiple sclerosis. *Chin J Pract Nerv Dis* 2014; 17: 68–69.

21. Wang J. Clinical characteristics and treatment analysis of 80 cases of multiple sclerosis. *Guide China Med* 2014; 12: 162–163.

22. Han M and Liu G. Analysis of clinical characteristics of 80 cases of multiple sclerosis. *China Foreign Med Treat* 2011; 30: 73.

23. Zheng X. Analysis of diagnosis and treatment of 83 cases of multiple sclerosis. *China Mod Med* 2013; 20: 174–177.

24. Wang J, Li C and Cui C. A retrospective analysis of clinical epidemiology of multiple sclerosis based on a single center. *J Sun Yat-sen Univ (Med Sci)* 2019; 40: 731–738.

25. Wang F. Clinical analysis of 10 patients with pediatric multiple sclerosis. *China Mod Med* 2012; 19: 165–166.

26. Cheng H, Xi J and Wang C. Clinical analysis of 15 patients with pediatric multiple sclerosis. *J Precis Med* 2018; 33: 505–511.

27. Ren C, Fang F and Lv J. Analysis of clinical characteristics of 31 patients with pediatric multiple sclerosis. *Chin J Pract Pediatr* 2014; 29: 266–271.

28. Li S, Zhang L and Zhou S. Analysis of clinical features and prognosis of 33 patients with pediatric multiple sclerosis. *Chin J Evid Based Pediatr* 2011; 6: 439–443.

29. Zhu H, Bao X and Zhang R. Clinical study of 84 patients with pediatric multiple sclerosis. *Chin J Pract Pediatr* 2016; 31: 51–55.

30. Duan G. *Clinical analysis of 9 patients with pediatric multiple sclerosis*. Qingdao University, 2018.

31. Gong Q. *Study on the influencing factors of early recurrence of patients with pediatric multiple sclerosis*. Chongqing Medical University, https://kns.cnki.net/KCMS/detail/detail.aspx?dbname=CMFD201701&filename=1016782171.nh (2017).

32. Jia C. *Analysis of cases and the correlation between the course of oral hormone therapy and the time of relapse of patients with pediatric multiple sclerosis*. Chongqing Medical University, https://kns.cnki.net/KCMS/detail/detail.aspx?dbname=CMFD202001&filename=1019659364.nh (2020).

33. Wang J and Wei S. Clinical characteristics and ocular manifestations visual involvement of pediatric multiple sclerosis. *China J Chin Ophthalmol* 2011; 3: 334–337.

34. Chen S. Study on the clinical characteristics and treatment plan of pediatric multiple sclerosis. *Guide China Med* 2017; 15: 58.

35. Duan G and Hua Q. Treatment and follow-up observation of pediatric multiple sclerosis. *Clin Focus* 2018; 33: 532–535.

36. Kong L. *Analysis of complications and related clinical features of relapsing-remitting multiple sclerosis and neuromyelitis optica spectrum diseases*. Chongqing Medical University, https://kns.cnki.net/KCMS/detail/detail.aspx?dbname=CMFD202001&filename=1019660252.nh (2020).

37. Zhang J. Analysis of clinical characteristics of 20 cases of multiple sclerosis. *Chin J Coal Ind Med* 2012; 15: 505–506.

38. He X and Zou J. Analysis of the diagnosis and treatment of 29 cases of multiple sclerosis. *Jilin Med J* 2012; 33: 1631–1632.

39. Liu J and Huang W. Clinical analysis of 34 cases of multiple sclerosis. *Guide China Med* 2013; 11: 120–121.

40. Li L and Zhou Y. Analysis of 39 cases of multiple sclerosis. *Chin J Misdiagn* 2012; 12: 1170–1171.

41. Qiu J. Analysis of clinical characteristics of 40 patients with multiple sclerosis. *Shanxi Med J* 2013; 42: 421–422.

42. Lin A, Li Z and Xu G. Clinical analysis of 54 cases of multiple sclerosis. *Fujian Med J* 2011; 33: 21–23.

43. Song L. Analysis of diagnosis and treatment of 58 cases of multiple sclerosis. *Chin J Misdiagn* 2011; 11: 1438.

44. Lin H, Gao X and Zhao X. Clinical treatment study of 60 cases of multiple sclerosis. *China Foreign Med Treat* 2013; 06: 49–50.

45. Zhao Y, Tan Y and Wang X. Analysis of 62 cases of multiple sclerosis. *Chin J Pract Nerv Dis* 2012; 15: 68–69.

46. Xu G. Clinical analysis of 70 cases of multiple sclerosis. *Guide China Med* 2012; 10: 453–454.

47. Liu P, Wu W and Liu S. MRI diagnosis analysis of 76 cases of multiple sclerosis. *Chin J Misdiagn* 2011; 11: 179.

48. Zhu J, Lin Y and Lu Y. Clinical manifestations in 82 patients with multiple sclerosis. *Chin Foreign Med Res* 2013; 11: 170–171.

49. Ma Y and Liu J. Clinical observation of 86 cases of multiple sclerosis. *Chin Community Doct* 2011; 13: 36.

50. Xue Y. *Comparison and analysis of the clinical features of multiple sclerosis and neuromyelitis optica*. Ningxia Medical University, https://kns.cnki.net/kcms/detail/detail.aspx?FileName=1016925000.nh&DbName=CMFD2017 (2017).

51. Xie Y, Li Y and Fu G. Clinical and spinal MRI analysis of multiple sclerosis and neuromyelitis optica spectrum disorders. *J Clin Radiol* 2020; 39: 879–884.

52. Chen P, Rao J and Dai Y. Analysis of the first manifestations of multiple sclerosis and neuromyelitis optica. *Shenzhen J Integr Tradit Chin West Med* 2016; 26: 8–9.

53. Hu M and Chang L. Clinical characteristics and misdiagnosis analysis of multiple sclerosis. *Anhui Med J* 2014; 35: 579–581.

54. Yang C and Yang Z. Comparative observation of early clinical characteristics of patients with multiple sclerosis and neuromyelitis optica high-risk syndrome. *Med Rec* 2015; 21: 1151–1152.

55. Lu L, Hong B and Shan G. Clinical analysis of 73 patients with multiple sclerosis. *Mod J Integr Tradit Chin West Med* 2013; 22: 2673–2675.

56. Zhang L. Clinical analysis of complications in patients with multiple sclerosis. *Guide China Med* 2013; 11: 190.

57. Liu R, Li Y and Du J. Study on clinical characteristics and influencing factors of self-care ability in patients with multiple sclerosis. *Heilongjiang J Tradit Chin Med* 2020; 49: 128.

58. Zhao W, Sun L and Yang Y. Analysis of clinical manifestations of patients with multiple sclerosis. *China J Pharm Econ* 2014; 9: 293–294.

59. Zhang Y, Li R and Du Y. Serum uric acid level in patients with multiple sclerosis and its correlation with the course of disease. *J Ningxia Med Univ* 2013; 85: 819–821.

60. Huang L and Chen H. Differencial analysis of gender in clinical characteristics of patients with multiple sclerosis. *Chin J Integr Med Cardio/Cerebrovasc Dis* 2018; 16: 367–369.

61. Su Y. Clinical analysis of 82 cases of multiple sclerosis. *Mod Hosp* 2012; 12: 54–55.

62. Hu L. MRI features and diagnostic value of multiple sclerosis. *West China Med J* 2015; 30: 1101–1104.

63. Ruan F. Clinical and MRI manifestations of multiple sclerosis. *Chin Community Doct* 2011; 13: 29.

64. Zeng M, Feng L and Li M. Observation on the clinical features of multiple sclerosis and the influencing factors of self-care ability. *Med Pharm J Chin People's Liberation Army* 2019; 31: 75–78.

65. Wang Q, Chu L and Guo L. Analysis of clinical characteristics of multiple sclerosis. *Chin J Pract Nerv Dis* 2015; 18: 29–30.

66. Chen Y, Zhou Y and Qin S. Analysis of clinical characteristics of multiple sclerosis. *Med Forum* 2012; 16: 2928–2929.

67. Meng R. Analysis of 12 cases of multiple sclerosis misdiagnosed as cerebral infarction. *Jilin Med J* 2012; 33: 3267–3268.

68. Zhou M and He B. The clinical effect of high-dose methylprednisolone in the treatment of multiple sclerosis. *Chin J Clin Ration Drug Use* 2020; 13: 84–85.

69. Wu B. Study on the effectiveness of interferon in the treatment of relapsing-remitting multiple sclerosis. *China Foreign Med Treat* 2016; 35: 126–128.

70. Zhou F and Luo B. Clinical features of early multiple sclerosis and neuromyelitis optica high-risk syndrome. *Chin J Pract Nerv Dis* 2015; 18: 22–24.

71. Zhang X, Tang Y and Xiao K. Analysis of clinical characteristics of late-onset multiple sclerosis. *J Pract Med* 2011; 27: 61–64.

72. He Y, Yang T and Jiang H. Analysis of clinical characteristics of multiple sclerosis with positive aquaporin 4 antibody. *Chin J Contemp Neurol Neurosurg* 2015; 15: 229–234.

73. Lv J. Clinical analysis of methylprednisolone pulse therapy combined with immunosuppressive agents in the treatment of multiple sclerosis. *J China Med Univ* 2015; 44: 89–91.

74. Li L. Effect of methylprednisone on the treatment of acute multiple sclerosis and neurological function score. *Clin J Chin Med* 2019; 11: 24–25.

75. Bai M. Analysis of the curative effect of methotrexate in the treatment of multiple sclerosis and neuromyelitis optica. *Chin J Neuroimmunol Neurol* 2017; 24: 435–437.

76. Yin K. *Analysis of disease progression and influencing factors of multiple sclerosis with a course of more than 10 years*. Hebei Medical University, https://kns.cnki.net/KCMS/detail/detail.aspx?dbname=CMFD201901&filename=1018859118.nh (2018).

77. Zhou J and Fu H. A comparative study on the pain characteristics of patients with neuromyelitis optica spectrum disorders and multiple sclerosis. *J North Sichuan Med Coll* 2019; 34: 32–35.

78. Ouyang G and Zhu H. Clinical features of multiple sclerosis in the elderly. *Shandong Med J* 2016; 56: 19–21.

79. Huang J, Huang W and Xiao C. Clinical analysis of 15 cases of spinal cord multiple sclerosis. *China J Pharm Econ* 2012; 03: 58–59.

80. Lin H. Clinical analysis of spinal cord multiple sclerosis. *Prev Treat Cardiovasc* 2013; 12: 93–94.

81. Xing J, Bo L and Qiong L. Clinical observation on treatment of 30 cases of multiple sclerosis with umbilical cord mesenchymal stem cells and rituximab. *Prog Mod Biomed* 2013; 13: 3307–3310.

82. Shi X. Clinical analysis of 24 cases of stroke-like multiple sclerosis. *Chin J Med Guide* 2016; 12: 342–343.

83. Wang S. The effect of methylprednisolone in patients with relapsing-remitting multiple sclerosis. *China Pract Med* 2017; 12: 96–98.

84. Feng L. *Retrospective study of neuromyelitis optica cases and comparison with multiple sclerosis.* Zhongshan University, https://d.wanfangdata.com.cn/thesis/Y1690498 (2010).

85. Han B. *The correlation analysis of clinical features between neuromyelitis optica spectrum disorders and multiple sclerosis.* Jilin University, 2019.

86. Chan KH, Tsang KL, Ho PW, *et al.* Clinical outcome of relapsing remitting multiple sclerosis among Hong Kong Chinese. *Clin Neurol Neurosurg* 2011; 113: 617–622.

87. Liu Y, Duan Y, Yu C, *et al.* Clinical isolated syndrome: a 3-year follow-up study in China. *Clin Neurol Neurosurg* 2011; 113: 658–660.

88. Chan KH, Lee R, Lee JCY, *et al.* Central nervous system inflammatory demyelinating disorders among Hong Kong Chinese. *J Neuroimmunol* 2013; 262: 100–105.

89. Long Y, Qiu W, Lu Z, *et al.* Clinical features of Chinese patients with multiple sclerosis with aquaporin-4 antibodies in cerebrospinal fluid but not serum. *J Clin Neurosci* 2013; 20: 233–237.

90. Yang CS, Zhang DQ, Wang JH, *et al.* Clinical features and sera anti-aquaporin 4 antibody positivity in patients with demyelinating disorders of the central nervous system from Tianjin, China. *CNS Neurosci Ther* 2014; 20: 32–39.

91. Li T, Xiao H, Li S, *et al.* Multiple sclerosis: clinical features and MRI findings in northern China. *Eur J Med Res* 2014; 19: 20.

92. Liu Y, Zhao G, Yu H, *et al.* Differentiation of neuromyelitis optica from multiple sclerosis in a cohort from the mainland of China. *Chin Med J* 2014; 127: 3213–3218.

93. Chen H, Liu SM, Zhang XX, *et al.* Clinical features of patients with multiple sclerosis and neuromyelitis optica spectrum disorders. *Chin Med J* 2016; 129: 2079–2084.

94. Liu X, Cui Y and Han J. Estimating epidemiological data of multiple sclerosis using hospitalized data in Shandong Province, China. *Orphanet J Rare Dis* 2016; 11: 73.

95. Zhang Y, Liu G, Han X, *et al.* The association of serum 25-hydroxyvitamin D levels with multiple sclerosis severity and progression in a case-control study from China. *J Neuroimmunol* 2016; 297: 127–131.

96. Lu T, Zhao L, Sun X, et al. Comparison of multiple sclerosis patients with and without oligoclonal IgG bands in South China. J Clin Neurosci 2019; 66: 51–55.

97. Fang CW, Wang HP, Chen HM, *et al.* Epidemiology and comorbidities of adult multiple sclerosis and neuromyelitis optica in Taiwan, 2001–2015. *Multiple Scler Relat Disord* 2020; 45: 102425.

98. Zhang Y, Xu Y, Xu T, *et al.* Prediction of long-term disability in Chinese patients with multiple sclerosis: a prospective cohort study. *Multiple Scler Relat Disord* 2020; 46: 102461.

99. Zhao L, Abrigo J, Chen Q, *et al.* Advanced MRI features in relapsing multiple sclerosis patients with and without CSF oligoclonal IgG bands. *Sci Rep* 2020; 10: 13703.

100. Zheng Y, Cai MT, Yang F, *et al.* IgG index revisited: diagnostic utility and prognostic value in multiple sclerosis. *Front Immunol* 2020; 11: 1799.

101. Xu L, Chen L, Wang S, *et al.* Urban prevalence of multiple sclerosis in China: a population-based study in six provinces. *Eur J Neurol* 2021; 28: 1636–1644.

102. Zhao Z, Zhang Y, Du Q, *et al.* Differences in physical, mental, and social functions between males and females in multiple sclerosis: a multicenter cross-sectional study in China. *Multiple Scler Relat Disord* 2021; 48: 102693.

103. Lai W, Kinoshita M, Peng A, *et al.* Does pregnancy affect women with multiple sclerosis? A prospective study in Western China. *J Neuroimmunol* 2018; 321: 24–28.

104. Negrotto L and Correale J. Evolution of multiple sclerosis prevalence and phenotype in Latin America. *Multiple Scler Relat Disord* 2018; 22: 97–102.

105. Forouhari A, Taheri G, Salari M, *et al.* Multiple sclerosis epidemiology in Asia and Oceania: a systematic review and meta-analysis. *Multiple Scler Relat Disord* 2021; 54: 103119.

106. Houzen H, Kondo K, Horiuchi K, *et al.* Consistent increase in the prevalence and female ratio of multiple sclerosis over 15 years in northern Japan. *Eur J Neurol* 2018; 25: 334–339.

107. Kim JE, Park SH, Han K, *et al.* Prevalence and incidence of neuromyelitis optica spectrum disorder and multiple sclerosis in Korea. *Mult Scler* 2020; 26: 1837–1844.

108. Shah Z, Wasay M, Chaudhry BZ, *et al.* Multiple sclerosis in Pakistan: current status and future perspective. *J Neurol Sci* 2020; 418: 117066.

109. Walton C, King R, Rechtman L, *et al.* Rising prevalence of multiple sclerosis worldwide:

insights from the Atlas of MS, third edition. *Mult Scler* 2020; 26: 1816–1821.

110. Cheng Q, Miao L, Zhang J, *et al*. A population-based survey of multiple sclerosis in Shanghai, China. *Neurology* 2007; 68: 1495–1500.

111. Lau KK, Wong WW, Sheng B, *et al*. The clinical course of multiple sclerosis patients in Hong Kong. *J Neurol Sci* 2008; 268: 78-82.

112. Tian DC, Zhang C, Yuan M, *et al*. Incidence of multiple sclerosis in China: a nationwide hospital-based study. *Lancet Reg Health West Pac* 2020; 1: 100010.

113. Altintas A, Dargvaniene J, Schneider-Gold C, *et al*. Gender issues of antibody-mediated diseases in neurology: (NMOSD/autoimmune encephalitis/MG). *Ther Adv Neurol Disord* 2020; 13: 1756286420949808.

114. Hor JY, Asgari N, Nakashima I, *et al*. Epidemiology of neuromyelitis optica spectrum disorder and its prevalence and incidence worldwide. *Front Neurol* 2020; 11: 501.

115. Papp V, Magyari M, Aktas O, *et al*. Worldwide incidence and prevalence of neuromyelitis optica: a systematic review. *Neurology* 2021; 96: 59–77.

116. Orton SM, Herrera BM, Yee IM, *et al*. Sex ratio of multiple sclerosis in Canada: a longitudinal study. *Lancet Neurol* 2006; 5: 932–936.

117. Izquierdo G, Venegas A, Sanabria C, *et al*. Long-term epidemiology of multiple sclerosis in the Northern Seville District. *Acta Neurol Scand* 2015; 132: 111–117.

118. Zsiros V, Fricska-Nagy Z, Füvesi J, *et al*. Prevalence of multiple sclerosis in Csongrád County, Hungary. *Acta Neurol Scand* 2014; 130: 277–282.

119. Viswanathan S, Rose N, Masita A, *et al*. Multiple sclerosis in malaysia: demographics, clinical features, and neuroimaging characteristics. *Mult Scler Int* 2013; 2013: 614716.

120. Siritho S and Prayoonwiwat N. A retrospective study of multiple sclerosis in Siriraj Hospital, Bankok, Thailand. *Can J Neurol Sci* 2007; 34: 99–104.

121. Farcomeni A, Cortese A, Sgarlata E, *et al*. The prevalence of multiple sclerosis in the metropolitan area of Rome: a capture-recapture analysis. *Neuroepidemiology* 2018; 50: 105–110.

122. Alroughani R, Ahmed SF, Behbehani R, *et al*. Increasing prevalence and incidence rates of multiple sclerosis in Kuwait. *Mult Scler* 2014; 20: 543–547.

123. Ascherio A and Munger KL. Epidemiology of multiple sclerosis: from risk factors to prevention – an update. *Semin Neurol* 2016; 36: 103–114.

124. Simpson S Jr, Blizzard L, Otahal P, *et al*. Latitude is significantly associated with the prevalence of multiple sclerosis: a meta-analysis. *J Neurol Neurosurg Psychiatry* 2011; 82: 1132–1141.

125. Hosseinzadeh A, Baneshi MR, Sedighi B, *et al*. Incidence of multiple sclerosis in Iran: a nationwide, population-based study. *Public Health* 2019; 175: 138–144.

126. Yamout B, Sahraian M, Bohlega S, *et al*. Consensus recommendations for the diagnosis and treatment of multiple sclerosis: 2019 revisions to the MENACTRIMS guidelines. *Multiple Scler Relat Disord* 2020; 37: 101459.

127. Alroughani R and Boyko A. Pediatric multiple sclerosis: a review. *BMC Neurol* 2018; 18: 27.

128. Yeshokumar AK, Narula S and Banwell B. Pediatric multiple sclerosis. *Curr Opin Neurol* 2017; 30: 216–221.

129. Kolčava J, Kočica J, Hulová M, *et al*. Conversion of clinically isolated syndrome to multiple sclerosis: a prospective study. *Multiple Scler Relat Disord* 2020; 44: 102262.

130. Vidal-Jordana A and Montalban X. Multiple sclerosis: epidemiologic, clinical, and therapeutic aspects. *Neuroimaging Clin N Am* 2017; 27: 195–204.

131. Lublin FD, Reingold SC, Cohen JA, *et al*. Defining the clinical course of multiple sclerosis: the 2013 revisions. *Neurology* 2014; 83: 278–286.

132. Inojosa H, Proschmann U, Akgün K, *et al*. A focus on secondary progressive multiple sclerosis (SPMS): challenges in diagnosis and definition. *J Neurol* 2021; 268: 1210–1221.

133. Rojas JI, Alonso Serena M, Garcea O, *et al*. Multiple sclerosis and neuromyelitis optica spectrum disorders in Argentina: comparing baseline data from the Argentinean MS Registry (RelevarEM). *Neurol Sci* 2020; 41: 1513–1519.

134. Yamout B, Barada W, Tohme RA, *et al*. Clinical characteristics of multiple sclerosis in Lebanon. *J Neurol Sci* 2008; 270: 88–93.

135. Cheng Q, Miao L, Zhang J, *et al*. Clinical features of patients with multiple sclerosis from a survey in Shanghai, China. *Mult Scler* 2008; 14: 671–678.

136. Olek MJ. Multiple sclerosis. *Ann Intern Med* 2021; 174: ITC81–ITC96.

137. Torres-Torres R and Sanchez-Dalmau BF. Treatment of acute optic neuritis and vision complaints in multiple sclerosis. *Curr Treat Options Neurol* 2015; 17: 328.

138. Cortese A, Conte A, Ferrazzano G, *et al.* Photophobia in multiple sclerosis. *Multiple Scler Relat Disord* 2018; 26: 55–57.

139. Ojeda E, Díaz-Cortes D, Rosales D, *et al.* Prevalence and clinical features of multiple sclerosis in Latin America. *Clin Neurol Neurosurg* 2013; 115: 381–387.

140. Rzepiński Ł, Zawadka-Kunikowska M, Maciejek Z, *et al.* Early clinical features, time to secondary progression, and disability milestones in Polish multiple sclerosis patients. *Medicinar* 2019; 55: 232.

141. Zakaria M, Zamzam DA, Abdel Hafeez MA, *et al.* Clinical characteristics of patients with multiple sclerosis enrolled in a new registry in Egypt. *Multiple Scler Relat Disord* 2016; 10: 30–35.

142. Bertado-Cortés B, Venzor-Mendoza C, Rubio-Ordoñez D, *et al.* Demographic and clinical characterization of multiple sclerosis in Mexico: the REMEMBer study. *Multiple Scler Relat Disord* 2020; 46: 102575.

143. Mesaros S, Drulović J and Lević Z. Clinical characteristics and neurophysiologic findings in patients with multiple sclerosis without oligoclonal IgG in cerebrospinal fluid. *Srp Arh Celok Lek* 2003; 131: 122–126.

144. Andreadou E, Chatzipanagiotou S, Constantinides VC, *et al.* Prevalence of cerebrospinal fluid oligoclonal IgG bands in Greek patients with clinically isolated syndrome and multiple sclerosis. *Clin Neurol Neurosurg* 2013; 115: 2094–2098.

145. Ellidag HY, Eren E, Erdogan N, *et al.* Comparison of neurophysiological and MRI findings of patients with multiple sclerosis using oligoclonal band technique. *Ann Neurosci* 2013; 20: 149–154.

146. Zhang JY, Shen XZ, Sun L, *et al.* Clinical and pathological features of acute optic neuritis in Chinese patients. *Chin Med J* 2013; 126: 1689–1692.

147. Katz Sand I. Classification, diagnosis, and differential diagnosis of multiple sclerosis. *Curr Opin Neurol* 2015; 28: 193–205.

148. Alroughani R, Ahmed SF and Al-Hashel J. Demographics and clinical characteristics of multiple sclerosis in Kuwait. *Eur Neurol* 2014; 72: 181–185.

149. Sundström P, Svenningsson A, Nyström L, *et al.* Clinical characteristics of multiple sclerosis in Västerbotten County in northern Sweden. *J Neurol Neurosurg Psychiatry* 2004; 75: 711–716.

150. Yamout B, El-Salem K, Gebeily S, *et al.* Multiple sclerosis in the Levant: a regional consensus statement. *Int J Neurosci* 2014; 124: 377–382.

151. Seyman E, Jones A, Guenette M, *et al.* Clinical and MRI characteristics of multiple sclerosis in patients of Middle Eastern and North African ancestry residing in Ontario, Canada. *Mult Scler* 2021; 27: 1027–1036.

152. Wasay M, Ali S, Khatri IA, *et al.* Multiple sclerosis in Pakistan. *Mult Scler* 2007; 13: 668–669.

153. Kim SH, Huh SY, Kim W, *et al.* Clinical characteristics and outcome of multiple sclerosis in Korea: does multiple sclerosis in Korea really differ from that in the Caucasian populations? *Mult Scler* 2013; 19: 1493–1498.

154. Singhal A, Bhatia R, Srivastava MV, *et al.* Multiple sclerosis in India: an institutional study. *Multiple Scler Relat Disord* 2015; 4: 250–257.

155. Cavenaghi VB, Dobrianskyj FM, Olival GSD, *et al.* Characterization of the first symptoms of multiple sclerosis in a Brazilian center: cross-sectional study. *Sao Paulo Med J* 2017; 135: 222–225.

156. Hoff JM, Dhayalan M, Midelfart A, *et al.* Visual dysfunction in multiple sclerosis. *Tidsskr Nor Laegeforen* 2019; 139.

157. Nij Bijvank JA, Petzold A, Coric D, *et al.* Saccadic delay in multiple sclerosis: a quantitative description. *Vision Res* 2020; 168: 33–41.

158. Kalincik T, Buzzard K, Jokubaitis V, *et al.* Risk of relapse phenotype recurrence in multiple sclerosis. *Mult Scler* 2014; 20: 1511–1522.

159. Wilkins A. Cerebellar dysfunction in multiple sclerosis. *Front Neurol* 2017; 8: 312.

160. Makhoul K, Ahdab R, Riachi N, *et al.* Tremor in multiple sclerosis: an overview and future perspectives. *Brain Sci* 2020; 10: 722.

161. Amato MP and Ponziani G. A prospective study on the prognosis of multiple sclerosis. *Neurol Sci* 2000; 21: S831–S838.

162. Etemadifar M, Nourian SM, Nourian N, *et al.* Early-onset multiple sclerosis in Isfahan, Iran:

report of the demographic and clinical features of 221 patients. *J Child Neurol* 2016; 31: 932–937.

163. Koch M, Mostert J, Heersema D, *et al*. Tremor in multiple sclerosis. *J Neurol* 2007; 254: 133–145.

164. Al-Abdullah MS and Siddiqui AF. Demographic and disease characteristics of multiple sclerosis in the Southwest Region of Saudi Arabia. *Neurosciences* 2018; 23: 320–325.

165. El-Salem K, Al-Shimmery E, Horany K, *et al*. Multiple sclerosis in Jordan: a clinical and epidemiological study. *J Neurol* 2006; 253: 1210–1216.

166. Amato MP, Zipoli V and Portaccio E. Cognitive changes in multiple sclerosis. *Expert Rev Neurother* 2008; 8: 1585–1596.

167. Højsgaard Chow H, Schreiber K, Magyari M, *et al*. Progressive multiple sclerosis, cognitive function, and quality of life. *Brain Behav* 2018; 8: e00875.

168. Patti F, Nicoletti A, Messina S, *et al*. Prevalence and incidence of cognitive impairment in multiple sclerosis: a population-based survey in Catania, Sicily. *J Neurol* 2015; 262: 923–930.

169. Nogales-Gaete J, Aracena R and Cepeda-Zumaeta S. Clinical features of 314 patients with relapsing-remitting multiple sclerosis. *Rev Med Chil* 2014; 142: 559–566.

170. Campbell J, Rashid W, Cercignani M, *et al*. Cognitive impairment among patients with multiple sclerosis: associations with employment and quality of life. *Postgrad Med J* 2017; 93: 143–147.

171. Vanotti S and Caceres FJ. Cognitive and neuropsychiatric disorders among MS patients from Latin America. *Mult Scler J Exp Transl Clin* 2017; 3: 2055217317717508.

172. Branco M, Ruano L, Portaccio E, *et al*. Aging with multiple sclerosis: prevalence and profile of cognitive impairment. *Neurol Sci* 2019; 40: 1651–1657.

173. Bodling AM, Denney DR and Lynch SG. Cognitive aging in patients with multiple sclerosis: a cross-sectional analysis of speeded processing. *Arch Clin Neuropsychol* 2009; 24: 761–767.

174. Khader HA, Emran B, Sulaimi MA, *et al*. Estimating the prevalence of cognition and mental health among multiple sclerosis patients: a population-based cross-sectional study. *Multiple Scler Relat Disord* 2019; 36: 101391.

175. Kim SH, Kwak K, Jeong IH, *et al*. Cognitive impairment differs between neuromyelitis optica spectrum disorder and multiple sclerosis. *Mult Scler* 2016; 22: 1850–1858.

176. Nourbakhsh B, Nunan-Saah J, Maghzi AH, *et al*. Longitudinal associations between MRI and cognitive changes in very early MS. *Multiple Scler Relat Disord* 2016; 5: 47–52.

177. Bustuchina Vlaicu M. Epilepsy in multiple sclerosis as a network disease. *Multiple Scler Relat Disord* 2019; 36: 101390.

178. Etemadifar M, Abtahi SH and Roomizadeh P. Epileptic seizures in multiple sclerosis: a population-based survey in Iran. *Acta Neurol Belg* 2013; 113: 271–278.

179. Neuß F, von Podewils F, Wang ZI, *et al*. Epileptic seizures in multiple sclerosis: prevalence, competing causes and diagnostic accuracy. *J Neurol* 2021; 268: 1721–1727.

180. Lo LMP, Taylor BV, Winzenberg T, *et al*. Change and onset-type differences in the prevalence of comorbidities in people with multiple sclerosis. *J Neurol* 2021; 268: 602–612.

181. Ajdacic-Gross V, Steinemann N, Horváth G, *et al*. Onset symptom clusters in multiple sclerosis: characteristics, comorbidities, and risk factors. *Front Neurol* 2021; 12: 693440.

182. Marrie RA, Reider N, Cohen J, *et al*. A systematic review of the incidence and prevalence of autoimmune disease in multiple sclerosis. *Mult Scler* 2015; 21: 282–293.

183. Exuzides A, Sheinson D, Sidiropoulos P, *et al*. Burden and cost of comorbidities in patients with neuromyelitis optica spectrum disorder. *J Neurol Sci* 2021; 427: 117530.

184. Magyari M, Koch-Henriksen N, Pfleger CC, *et al*. Gender and autoimmune comorbidity in multiple sclerosis. *Mult Scler* 2014; 20: 1244–1251.

185. Maric GD, Pekmezovic TD, Mesaros ST, *et al*. The prevalence of comorbidities in patients with multiple sclerosis: population-based registry data. *Neurol Sci* 2021; 42: 1887–1893.

186. Marrie RA. Comorbidity in multiple sclerosis: past, present and future. *Clin Invest Med* 2019; 42: E5–E12.

187. Jick SS, Li L, Falcone GJ, *et al*. Epidemiology of multiple sclerosis: results from a large observational study in the UK. *J Neurol* 2015; 262: 2033–2041.

188. Tettey P, Siejka D, Simpson S Jr, *et al.* Frequency of comorbidities and their association with clinical disability and relapse in multiple sclerosis. *Neuroepidemiology* 2016; 46: 106–113.

189. Kang JH, Chen YH and Lin HC. Comorbidities amongst patients with multiple sclerosis: a population-based controlled study. *Eur J Neurol* 2010; 17: 1215–1219.

190. Sicras-Mainar A, Ruíz-Beato E, Navarro-Artieda R, *et al.* Comorbidity and metabolic syndrome in patients with multiple sclerosis from Asturias and Catalonia, Spain. *BMC Neurol* 2017; 17: 134.

191. Ciampi E, Uribe-San-Martin R, Soler B, *et al.* Prevalence of comorbidities in multiple sclerosis and impact on physical disability according to disease phenotypes. *Multiple Scler Relat Disord* 2020; 46: 102565.

192. Kapica-Topczewska K, Tarasiuk J, Chorąży M, *et al.* The epidemiology of comorbidities among multiple sclerosis patients in northeastern Poland. *Multiple Scler Relat Disord* 2020; 41: 102051.

193. Ostolaza A, Corroza J and Ayuso T. Multiple sclerosis and aging: comorbidity and treatment challenges. *Multiple Scler Relat Disord* 2021; 50: 102815.

194. Rot U and Mesec A. Clinical, MRI, CSF and electrophysiological findings in different stages of multiple sclerosis. *Clin Neurol Neurosurg* 2006; 108: 271–274.

195. Gasperi C, Salmen A, Antony G, *et al.* Association of intrathecal immunoglobulin G synthesis with disability worsening in multiple sclerosis. *JAMA Neurol* 2019; 76: 841–849.

196. Olsson JE and Pettersson B. A comparison between agar gel electrophoresis and CSF serum quotients of IgG and albumin in neurological disease. *Acta Neurol Scand* 1976; 53: 308–322.

197. Becker M, Latarche C, Roman E, *et al.* No prognostic value of routine cerebrospinal fluid biomarkers in a population-based cohort of 407 multiple sclerosis patients. *BMC Neurol* 2015; 15: 79.

198. Sladkova V, Mares J, Hlustik P, *et al.* Intrathecal synthesis in particular types of multiple sclerosis. *Biomed Pap Med Fac Univ Palacky Olomouc Czech Repub* 2014; 158: 124–126.

199. Imrell K, Landtblom AM, Hillert J, *et al.* Multiple sclerosis with and without CSF bands: clinically indistinguishable but immunogenetically distinct. *Neurology* 2006; 67: 1062–1064.

200. Watanabe M, Nakamura Y, Sato S, *et al.* HLA genotype-clinical phenotype correlations in multiple sclerosis and neuromyelitis optica spectrum disorders based on Japan MS/NMOSD Biobank data. *Sci Rep* 2021; 11: 607.

201. Belman AL, Krupp LB, Olsen CS, *et al.* Characteristics of children and adolescents with multiple sclerosis. *Pediatrics* 2016; 138: e20160120.

202. Imrell K, Greiner E, Hillert J, *et al.* HLA-DRB115 and cerebrospinal-fluid-specific oligoclonal immunoglobulin G bands lower age at attainment of important disease milestones in multiple sclerosis. *J Neuroimmunol* 2009; 210: 128–130.

203. Siritho S and Freedman MS. The prognostic significance of cerebrospinal fluid in multiple sclerosis. *J Neurol Sci* 2009; 279: 21–25.

204. Dobson R, Ramagopalan S, Davis A, *et al.* Cerebrospinal fluid oligoclonal bands in multiple sclerosis and clinically isolated syndromes: a meta-analysis of prevalence, prognosis and effect of latitude. *J Neurol Neurosurg Psychiatry* 2013; 84: 909–914.

205. Lechner-Scott J, Spencer B, de Malmanche T, *et al.* The frequency of CSF oligoclonal banding in multiple sclerosis increases with latitude. *Mult Scler* 2012; 18: 974–982.

206. Negrotto L, Marrodan M, Fiol M, *et al.* Absence of latitudinal gradient in oligoclonal bands prevalence in Argentina. *Multiple Scler Relat Disord* 2020; 46: 102582.

207. Pandya S, Kaunzner UW, Hurtado Rúa SM, *et al.* Impact of lesion location on longitudinal myelin water fraction change in chronic multiple sclerosis lesions. *J Neuroimaging* 2020; 30: 537–543.

208. Barkhof F, Simon JH, Fazekas F, *et al.* MRI monitoring of immunomodulation in relapse-onset multiple sclerosis trials. *Nat Rev Neurol* 2011; 8: 13–21.

209. Akaishi T, Takahashi T and Nakashima I. Oligoclonal bands and periventricular lesions in multiple sclerosis will not increase blood-brain barrier permeability. *J Neurol Sci* 2018; 387: 129–133.

210. Silveira F, Pappolla A, Sánchez F, *et al.* Brain magnetic resonance imaging features in multiple sclerosis and neuromyelitis optica spectrum disorders patients with or without aquaporin-4

antibody in a Latin American population. *Multiple Scler Relat Disord* 2020; 42: 102049.

211. Brex PA, O'Riordan JI, Miszkiel KA, *et al.* Multisequence MRI in clinically isolated syndromes and the early development of MS. *Neurology* 1999; 53: 1184–1190.

212. Gaetani L, Fanelli F, Riccucci I, *et al.* High risk of early conversion to multiple sclerosis in clinically isolated syndromes with dissemination in space at baseline. *J Neurol Sci* 2017; 379: 236–240.

213. Filippi M, Preziosa P, Meani A, *et al.* Prediction of a multiple sclerosis diagnosis in patients with clinically isolated syndrome using the 2016 MAGNIMS and 2010 McDonald criteria: a retrospective study. *Lancet Neurol* 2018; 17: 133–142.

214. Filippi M, Rocca MA, Calabrese M, *et al.* Intracortical lesions: relevance for new MRI diagnostic criteria for multiple sclerosis. *Neurology* 2010; 75: 1988–1994.

215. Scalfari A, Romualdi C, Nicholas RS, *et al.* The cortical damage, early relapses, and onset of the progressive phase in multiple sclerosis. *Neurology* 2018; 90: e2107–e2118.

216. Pisani AI, Scalfari A, Crescenzo F, *et al.* A novel prognostic score to assess the risk of progression in relapsing-remitting multiple sclerosis patients. *Eur J Neurol* 2021; 28: 2503–2512.

217. Vural G, Keklikoğlu HD, Temel Ş, *et al.* Comparison of double inversion recovery and conventional magnetic resonance brain imaging in patients with multiple sclerosis and relations with disease disability. *Neuroradiol J* 2013; 26: 133–142.

218. Akhtar N, Elsetouhy A, Deleu D, *et al.* Newly diagnosed multiple sclerosis in state of Qatar. *Clin Neurol Neurosurg* 2013; 115: 1333–1337.

219. Thompson AJ, Banwell BL, Barkhof F, *et al.* Diagnosis of multiple sclerosis: 2017 revisions of the McDonald criteria. *Lancet Neurol* 2018; 17: 162–173.

220. Fazekas F, Offenbacher H, Fuchs S, *et al.* Criteria for an increased specificity of MRI interpretation in elderly subjects with suspected multiple sclerosis. *Neurology* 1988; 38: 1822–1825.

221. Lu Z, Zhang B, Qiu W, *et al.* Comparative brain stem lesions on MRI of acute disseminated encephalomyelitis, neuromyelitis optica, and multiple sclerosis. *PLoS One* 2011; 6: e22766.

222. Renard D, Castelnovo G, Bousquet PJ, *et al.* Brain MRI findings in long-standing and disabling multiple sclerosis in 84 patients. *Clin Neurol Neurosurg* 2010; 112: 286–290.

223. Kira J, Tobimatsu S, Goto I, *et al.* Primary progressive versus relapsing remitting multiple sclerosis in Japanese patients: a combined clinical, magnetic resonance imaging and multimodality evoked potential study. *J Neurol Sci* 1993; 117: 179–185.

224. Minneboo A, Barkhof F, Polman CH, *et al.* Infratentorial lesions predict long-term disability in patients with initial findings suggestive of multiple sclerosis. *Arch Neurol* 2004; 61: 217–221.

225. Skorić MK, Adamec I, Mađarić VN, *et al.* Evaluation of brainstem involvement in multiple sclerosis. *Can J Neurol Sci* 2014; 41: 346–349.

226. Nakashima I, Fujihara K, Okita N, *et al.* Clinical and MRI study of brain stem and cerebellar involvement in Japanese patients with multiple sclerosis. *J Neurol Neurosurg Psychiatry* 1999; 67: 153–157.

227. Hannoun S, Heidelberg D, Hourani R, *et al.* Diagnostic value of 3DFLAIR in clinical practice for the detection of infratentorial lesions in multiple sclerosis in regard to dual echo T2 sequences. *Eur J Radiol* 2018; 102: 146–151.

228. Sastre-Garriga J, Tintoré M, Rovira A, *et al.* Conversion to multiple sclerosis after a clinically isolated syndrome of the brainstem: cranial magnetic resonance imaging, cerebrospinal fluid and neurophysiological findings. *Mult Scler* 2003; 9: 39–43.

229. Thorpe JW, Kidd D, Moseley IF, *et al.* Serial gadolinium-enhanced MRI of the brain and spinal cord in early relapsing-remitting multiple sclerosis. *Neurology* 1996; 46: 373–378.

230. Shibasaki H, McDonald WI and Kuroiwa Y. Racial modification of clinical picture of multiple sclerosis: comparison between British and Japanese patients. *J Neurol Sci* 1981; 49: 253–271.

231. Bansil S, Singhal BS, Ahuja GK, *et al.* Comparison between multiple sclerosis in India and the United States: a case-control study. *Neurology* 1996; 46: 385–387.

232. Valsasina P, Aboulwafa M, Preziosa P, *et al.* Cervical cord T1-weighted hypointense lesions at MR imaging in multiple sclerosis: relationship to cord atrophy and disability. *Radiology* 2018; 288: 234–244.

233. Tench CR, Morgan PS, Jaspan T, *et al*. Spinal cord imaging in multiple sclerosis. *J Neuroimaging* 2005; 15: 94S–102S.

234. Lycklama à Nijeholt GJ, Barkhof F, Scheltens P, *et al*. MR of the spinal cord in multiple sclerosis: relation to clinical subtype and disability. *AJNR Am J Neuroradiol* 1997; 18: 1041–1048.

235. Jacobi C, Hähnel S, Martinez-Torres F, *et al*. Prospective combined brain and spinal cord MRI in clinically isolated syndromes and possible early multiple sclerosis: impact on dissemination in space and time. *Eur J Neurol* 2008; 15: 1359–1364.

236. Lukas C, Sombekke MH, Bellenberg B, *et al*. Relevance of spinal cord abnormalities to clinical disability in multiple sclerosis: MR imaging findings in a large cohort of patients. *Radiology* 2013; 269: 542–552.

237. Petrova N, Carassiti D, Altmann DR, *et al*. Axonal loss in the multiple sclerosis spinal cord revisited. *Brain Pathol* 2018; 28: 334–348.

238. Petrova N, Nutma E, Carassiti D, *et al*. Synaptic loss in multiple sclerosis spinal cord. *Ann Neurol* 2020; 88: 619–625.

239. Thorpe JW, Kidd D, Kendall BE, *et al*. Spinal cord MRI using multi-array coils and fast spin echo. I. Technical aspects and findings in healthy adults. *Neurology* 1993; 43: 2625–2631.

240. Bot JC, Barkhof F, Polman CH, *et al*. Spinal cord abnormalities in recently diagnosed MS patients: added value of spinal MRI examination. *Neurology* 2004; 62: 226–233.

241. Weier K, Mazraeh J, Naegelin Y, *et al*. Biplanar MRI for the assessment of the spinal cord in multiple sclerosis. *Mult Scler* 2012; 18: 1560–1569.

242. Breckwoldt MO, Gradl J, Hähnel S, *et al*. Increasing the sensitivity of MRI for the detection of multiple sclerosis lesions by long axial coverage of the spinal cord: a prospective study in 119 patients. *J Neurol* 2017; 264: 341–349.

243. Lee SS, Sohn EH and Nam SW. Preliminary studies on the clinical features of multiple sclerosis in Korea. *J Clin Neurol* 2006; 2: 231–237.

244. Lau KK, Lee PO, Chan KY, *et al*. Interferon treatment for multiple sclerosis patients in Hong Kong. *Hong Kong Med J* 2000; 6: 221–223.

245. Miller AE and Calabresi PA. Central vein sign in multiple sclerosis: ready for front and center? *Neurology* 2018; 90: 631–632.

246. Sati P, Oh J, Constable RT, *et al*. The central vein sign and its clinical evaluation for the diagnosis of multiple sclerosis: a consensus statement from the North American Imaging in Multiple Sclerosis Cooperative. *Nat Rev Neurol* 2016; 12: 714–722.

247. Tallantyre EC, Dixon JE, Donaldson I, *et al*. Ultra-high-field imaging distinguishes MS lesions from asymptomatic white matter lesions. *Neurology* 2011; 76: 534–539.

248. Sparacia G, Agnello F, Gambino A, *et al*. Multiple sclerosis: high prevalence of the 'central vein' sign in white matter lesions on susceptibility-weighted images. *Neuroradiol J* 2018; 31: 356–361.

249. Maggi P, Absinta M, Grammatico M, *et al*. Central vein sign differentiates multiple sclerosis from central nervous system inflammatory vasculopathies. *Ann Neurol* 2018; 83: 283–294.

250. Chawla S, Kister I, Wuerfel J, *et al*. Iron and non-iron-related characteristics of multiple sclerosis and neuromyelitis optica lesions at 7T MRI. *AJNR Am J Neuroradiol* 2016; 37: 1223–1230.

251. Kilsdonk ID, Lopez-Soriano A, Kuijer JP, *et al*. Morphological features of MS lesions on FLAIR* at 7 T and their relation to patient characteristics. *J Neurol* 2014; 261: 1356–1364.

252. Kuchling J, Ramien C, Bozin I, *et al*. Identical lesion morphology in primary progressive and relapsing–remitting MS – an ultrahigh field MRI study. *Mult Scler* 2014; 20: 1866–1871.

253. Tan IL, van Schijndel RA, Pouwels PJ, *et al*. MR venography of multiple sclerosis. *AJNR Am J Neuroradiol* 2000; 21: 1039–1042.

254. Hammond KE, Metcalf M, Carvajal L, *et al*. Quantitative in vivo magnetic resonance imaging of multiple sclerosis at 7 Tesla with sensitivity to iron. *Ann Neurol* 2008; 64: 707–713.

255. Stankiewicz JM, Neema M and Ceccarelli A. Iron and multiple sclerosis. *Neurobiol Aging* 2014; 35: S51–S58.

256. Khalil M, Langkammer C, Pichler A, *et al*. Dynamics of brain iron levels in multiple sclerosis: a longitudinal 3T MRI study. *Neurology* 2015; 84: 2396–2402.

257. Dal-Bianco A, Grabner G, Kronnerwetter C, *et al*. Slow expansion of multiple sclerosis iron rim lesions: pathology and 7 T magnetic resonance imaging. *Acta Neuropathol* 2017; 133: 25–42.

258. Burgetova A, Dusek P, Vaneckova M, *et al*. Thalamic iron differentiates primary-progressive and relapsing-remitting multiple sclerosis. *AJNR Am J Neuroradiol* 2017; 38: 1079–1086.

259. Bagnato F, Hametner S, Yao B, *et al.* Tracking iron in multiple sclerosis: a combined imaging and histopathological study at 7 Tesla. *Brain* 2011; 134: 3602–3615.

260. Llufriu S, Pujol T, Blanco Y, *et al.* T2 hypointense rims and ring-enhancing lesions in MS. *Mult Scler* 2010; 16: 1317–1325.

261. Yao B, Ikonomidou VN, Cantor FK, *et al.* Heterogeneity of multiple sclerosis white matter lesions detected with T2*-weighted imaging at 7.0 Tesla. *J Neuroimaging* 2015; 25: 799–806.

262. Luchetti S, Fransen NL, van Eden CG, *et al.* Progressive multiple sclerosis patients show substantial lesion activity that correlates with clinical disease severity and sex: a retrospective autopsy cohort analysis. *Acta Neuropathol* 2018; 135: 511–528.

263. Chen X, Zeng C, Luo T, *et al.* Iron deposition of the deep grey matter in patients with multiple sclerosis and neuromyelitis optica: a control quantitative study by 3D-enhanced susceptibility-weighted angiography (ESWAN). *Eur J Radiol* 2012; 81: e633–e639.

264. Wuerfel J, Sinnecker T, Ringelstein EB, *et al.* Lesion morphology at 7 Tesla MRI differentiates Susac syndrome from multiple sclerosis. *Mult Scler* 2012; 18: 1592–1599.

265. Sinnecker T, Clarke MA, Meier D, *et al.* Evaluation of the central vein sign as a diagnostic imaging biomarker in multiple sclerosis. *JAMA Neurol* 2019; 76: 1446–1456.

266. Maggi P, Sati P, Nair G, *et al.* Paramagnetic rim lesions are specific to multiple sclerosis: an international multicenter 3T MRI study. *Ann Neurol* 2020; 88: 1034–1042.

267. Blindenbacher N, Brunner E, Asseyer S, *et al.* Evaluation of the 'ring sign' and the 'core sign' as a magnetic resonance imaging marker of disease activity and progression in clinically isolated syndrome and early multiple sclerosis. *Mult Scler J Exp Transl Clin* 2020; 6: 2055217320915480.

268. Calvi A, Haider L, Prados F, *et al.* In vivo imaging of chronic active lesions in multiple sclerosis. *Mult Scler* 2022; 28: 683–690.

269. Zhou R, Zeng Q, Yang H, *et al.* Status of immunotherapy acceptance in Chinese patients with multiple sclerosis: analysis of multiple sclerosis patient survival report 2018. *Front Neurol* 2021; 12: 651511.

270. Yamout B, Alroughani R, Al-Jumah M, *et al.* Consensus guidelines for the diagnosis and treatment of multiple sclerosis. *Curr Med Res Opin* 2013; 29: 611–621.

271. Filippi M, Bar-Or A, Piehl F, *et al.* Multiple sclerosis. *Nat Rev Dis Primers* 2018; 4: 43.

272. China expert consensus on multiple sclerosis diagnosis and treatment (2018). *Chin J Neurol* 2018; 25: 387–394.

273. Song T, Chang H, Du L, *et al.* Glucocorticoid receptor mutations and clinical sensitivity to glucocorticoid in Chinese multiple sclerosis patients. *Neurol Sci* 2020; 41: 2767–2771.

274. Frohman EM, Brannon K, Racke MK, *et al.* Mycophenolate mofetil in multiple sclerosis. *Clin Neuropharmacol* 2004; 27: 80–83.

275. Massacesi L, Parigi A, Barilaro A, *et al.* Efficacy of azathioprine on multiple sclerosis new brain lesions evaluated using magnetic resonance imaging. *Arch Neurol* 2005; 62: 1843–1847.

276. Milanese C, La Mantia L, Salmaggi A, *et al.* A double blind study on azathioprine efficacy in multiple sclerosis: final report. *J Neurol* 1993; 240: 295–298.

277. Goodkin DE, Bailly RC, Teetzen ML, *et al.* The efficacy of azathioprine in relapsing-remitting multiple sclerosis. *Neurology* 1991; 41: 20–25.

278. Casetta I, Iuliano G and Filippini G. Azathioprine for multiple sclerosis. *Cochrane Database Syst Rev* 2007; 2007: CD003982.

279. Michel L, Vukusic S, De Seze J, *et al.* Mycophenolate mofetil in multiple sclerosis: a multicentre retrospective study on 344 patients. *J Neurol Neurosurg Psychiatry* 2014; 85: 279–283.

280. Goodin DS. Interferon-beta therapy in multiple sclerosis: evidence for a clinically relevant dose response. *Drugs* 2001; 61: 1693–1703.

281. Bar-Or A, Pachner A, Menguy-Vacheron F, *et al.* Teriflunomide and its mechanism of action in multiple sclerosis. *Drugs* 2014; 74: 659–674.

282. Qiu W, Huang DH, Hou SF, *et al.* Efficacy and safety of teriflunomide in Chinese patients with relapsing forms of multiple sclerosis: a subgroup analysis of the phase 3 TOWER study. *Chin Med J* 2018; 131: 2776–2784.

283. Xu Y, Mao N, Chirikov V, *et al.* Cost-effectiveness of teriflunomide compared to interferon beta-1b for relapsing multiple sclerosis patients in China. *Clin Drug Investig* 2019; 39: 331–340.

284. Petrou P, Kassis I, Levin N, *et al.* Beneficial effects of autologous mesenchymal stem cell transplantation in active progressive multiple sclerosis. *Brain* 2020; 143: 3574–3588.