Fast Facts: Multiple Sclerosis

Fourth edition

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Declaration of Independence
This book is as balanced and as practical as we can make it.
Ideas for improvement are always welcome: feedback@fastfacts.com
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List of abbreviations

ACE: angiotensin-converting enzyme (inhibitor)
ACTH: adrenocorticotropic hormone
ADEM: acute disseminated encephalomyelitis
AHSCT: autologous hematopoietic stem cell transplantation
APC: advanced practice clinician
AQP-4: aquaporin-4
ASA: acetylsalicylic acid (aspirin)
CBC: complete blood count
CIS: clinically isolated syndrome
CNS: central nervous system
CSF: cerebrospinal fluid
DIS: dissemination in space
DIT: dissemination in time
DMT: disease-modifying treatment
EBV: Epstein–Barr virus
EDSS: Expanded Disability Status Scale
EMG: electromyography
ENA: extractable nuclear antigen
FBC: full blood count
FDG-PET: fludeoxyglucose positron emission tomography
FLAIR: fluid attenuated inversion recovery (imaging)
IFNβ: interferon-beta
Ig: immunoglobulin
INO: internuclear ophthalmoplegia
HLA: human leukocyte antigen
LETM: longitudinally extensive transverse myelitis
LFT: liver function test
MHC: major histocompatibility complex
MRI: magnetic resonance imaging
MS: multiple sclerosis
MSFC: Multiple Sclerosis Functional Composite
NMO: neuromyelitis optica
NSAID: non-steroidal anti-inflammatory drug
PLEX: plasma exchange
PML: progressive multifocal leukoencephalopathy
RAPD: relative afferent pupillary defect
SLE: systemic lupus erythematosus
STIR: short time inversion recovery (imaging)
UV: ultraviolet
**Introduction**

Multiple sclerosis (MS) affects people in the most productive period of their lives, affecting quality of life, family and career. MS produces both physical and neuropsychiatric effects, and carries considerable individual and societal economic burden.

Since the last edition of this book, ‘no evidence of disease activity’ (NEDA), or ‘freedom from disease activity’ has been proposed as a new treatment target in MS. NEDA is defined as no relapses, no increase in disability or no new or active (enhancing) lesions on MRI. The first pharmaceutical products for progressive MS and the first remyelination trial have shown positive effects on nerve repair, and for the youngest patients with MS, some of the risk factors have been elucidated. These developments may herald a new era for MS management. Coupled with recent developments in imaging, they are helping clinicians to diagnose and potentially treat MS in the earliest phases of the disease.

In this new edition of *Fast Facts: Multiple Sclerosis* we hope to emphasize the sense of optimism embodied by these advances. Here, we present the latest evidence on disease pathomechanisms, clinical aspects and modern diagnostic criteria, and review novel therapies that have been recently incorporated into an expanding MS treatment armamentarium. We also emphasize the importance of multidisciplinary management in patients with MS, and with this in mind have written this handbook for the benefit of all healthcare professionals involved in the care of patients with this complex disease.

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Multiple sclerosis (MS) is a neurological condition resulting from inflammation and degeneration within the central nervous system (CNS). This inflammation can affect different sites at different times, producing a variety of symptoms and signs. In the early stages there are periods of relapse and remission, and in most patients a slowly progressive course ensues within one to two decades of disease onset. The cause of MS is unknown, but dysregulation of the immune system is central to the pathogenesis of the disease.

**Epidemiology**

MS is the leading cause of neurological disability in the young and middle-aged populations of the developed world. Survey figures from 2013 suggest that it affects around 100,000 people in the UK, 21,000 in Australia and 400,000 in the USA, and an estimated 2.3 million people worldwide. This is likely to be a significant underestimate as there is little published information on populations in many countries.

**Prevalence.** The number of people with MS in a given population at any one time is usually expressed as cases per 100,000 population. MS is most prevalent in northern European Caucasian populations, especially individuals of Nordic descent, and is notably more prevalent in temperate than equatorial regions. The worldwide prevalence of MS appears to be increasing: this is related to many factors, including earlier diagnosis, an aging population and a true increase in disease incidence, especially in females.

Prevalence varies worldwide and in some countries exceeds 250 per 100,000. Globally, the median estimated prevalence of MS is 33 per 100,000. Regionally, the median estimated prevalence of MS is greatest in North America and Europe (140 and 108 per 100,000, respectively). The estimated prevalence is 164 per 100,000 people in the UK, 95.6 per 100,000 in Australia and 135 per 100,000 in the USA. Prevalence varies significantly both within regions and within countries.
**Incidence.** The number of new cases per 100 000 population per year can indicate changes in the risk of a disease within a population, and can signify whether the disease frequency is increasing in a population. It is not affected by changes in survival. The incidence of MS, which peaks at age 30, appears to be rising in both the northern and southern hemispheres, particularly in women. The median estimated global incidence of MS is 2.5 per 100 000 per year, but in some countries the incidence may exceed 10 per 100 000 per year.

**Geo-epidemiology of MS.** The prevalence of MS is significantly associated with latitude, particularly in populations of European descent (Figure 1.1). The ‘latitudinal gradient’ in MS has been confirmed by independent studies in Australia, New Zealand and the USA, with exceptions in Sardinia and northern Scandinavia. In Australia, the prevalence in Tasmania is six times greater than that in northern Queensland. Genetic variation between geographically

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**Figure 1.1** Geographic distribution of MS, showing a greater prevalence at high latitudes. Source: Atlas of MS Database. Multiple Sclerosis International Federation, 2013. www.atlasofms.org, last accessed 18 May 2016.
The neuropathological examination of affected brain and spinal cord tissue has driven multiple sclerosis (MS) research for more than 170 years, and in large part has shaped concepts of pathogenesis, tissue injury and repair. In contrast to gray matter, which contains neural cell bodies, white matter predominantly contains myelinated axon tracts. MS is characterized by the presence of multifocal lesions or ‘plaques’, predominantly in the white matter, which exhibit myelin destruction, perivascular inflammation and relative preservation of axons. It is now recognized that there is considerable gray matter involvement in MS as well as diffuse white matter pathology that contributes to long-standing disability.

The condition is traditionally regarded as a T-cell-mediated inflammatory demyelinating disease, initiated outside the central nervous system (CNS) by loss of tolerance to one, or a number of, CNS antigen(s). This hypothesis is now regarded as an oversimplification, and neuropathological, biomarker and treatment studies have implicated B cells, regulatory T cells and factors within the CNS as critical pathophysiological determinants.

**Lesion distribution**
The number, size and distribution of lesions vary widely amongst individuals with MS. In early disease most patients have small circumscribed lesions that typically occur in the periventricular and subcortical white matter, corpus callosum, optic nerves, cerebellum and spinal cord (Figure 2.1). Nowadays, more diffuse white matter pathology and early gray matter lesions are being seen using new MRI techniques, as well as in pathological studies. The whole brain volume loss seen early in the course of MS is likely to be associated with these diffuse as well as discrete changes of MS that lead to brain atrophy.

Although disease may be macroscopically confined to the white matter, careful neuropathological evaluation reveals focal cortical and deep gray matter lesions in almost all patients with MS (Figure 2.2).
**Figure 2.1** Whole brain coronal section from a patient with secondary progressive MS. Typical small chronic lesions are present in the corpus callosum (asterisk) and periventricular white matter (arrow) of both hemispheres. Remyelinated lesions, which stain palely for myelin, are also present (arrowhead). Small leukocortical lesions are visible at higher power in both hemispheres. Luxol fast-blue.

**Figure 2.2** The edge of a chronically demyelinated cortical lesion, which also involves the adjacent white matter, in a patient with secondary progressive MS. Note the reduction in neuronal density in the demyelinated (upper) zone of gray matter. Luxol fast-blue cresyl violet.