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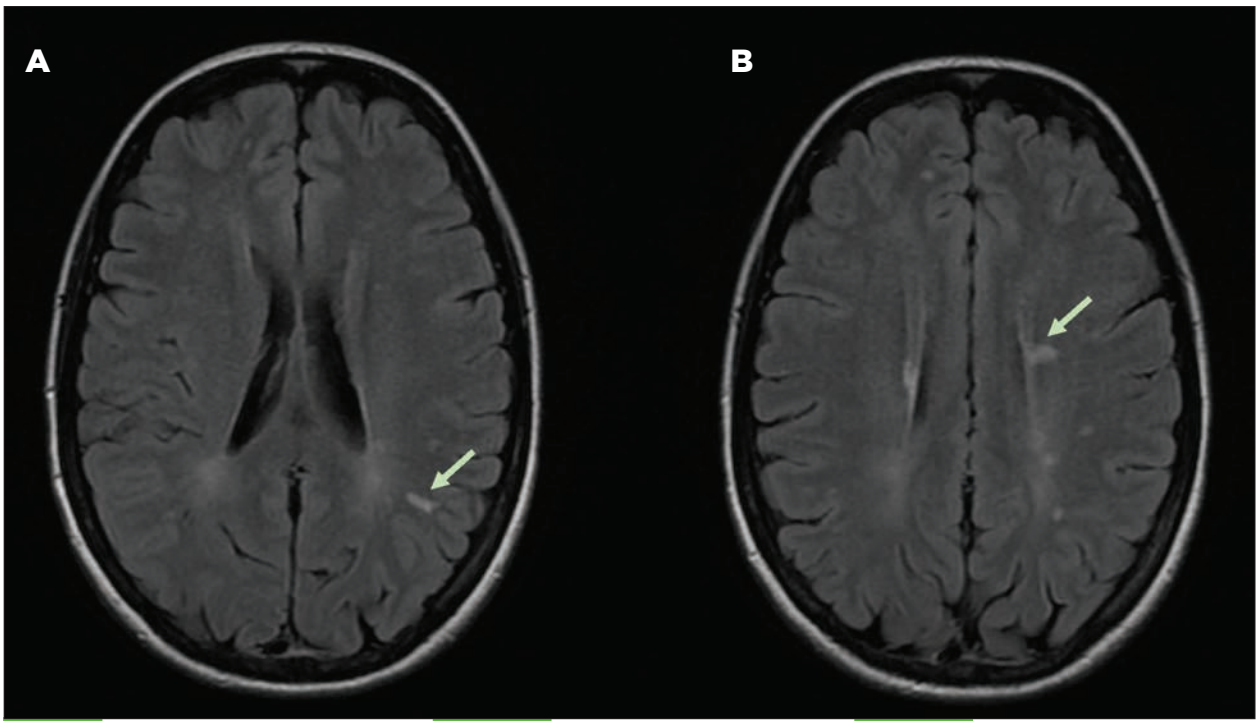

FIGURE 1
MRI scan of an MS patient at diagnosis showing two typical examples of MS lesions:
A A juxtacortical lesion and
B A periventricular lesion perpendicular to the corpus callosum (Dawson's fingers)

How do patients with MS present in primary care?

MULTIPLE SCLEROSIS (MS) IS THE LEADING CAUSE OF NON-TRAUMATIC NEUROLOGICAL DISABILITY in young adults.[1,2]

Diagnosis is based on the evidence of neurological symptoms, and aided by magnetic resonance imaging (MRI), e.g. white and grey matter changes in the brain and spinal cord, and CSF analysis, e.g. presence of oligoclonal bands.[3] Once diagnosed, people with MS require lifelong management usually involving a range of healthcare professionals.[4]

In the UK, MS prevalence increased by 28%, from 1990 to 2016, due to earlier diagnosis and increased survival.[2,5] Public Health England estimates that the 2018 prevalence in England was 190 cases per 100,000, with 105,800 affected individuals.[6]

The female to male ratio is 2:1, and patients have a minimally reduced life expectancy.[1,2]

What are the different phenotypes?

CLINICAL PRESENTATION

Over the past few decades, the natural history of MS has progressively become milder,[7] mainly as a result of advances in diagnosis and treatment. In particular, early recognition of MS symptoms and referral to MS specialists has contributed to improved long-term prognosis, and better management before irreversible disability accrues.[8]

In most cases, clinical presentation is characterised by recurring episodes of neurological deficit i.e. relapses. A relapse is defined as the acute-subacute onset of neurological symptoms lasting at least 24 hours, in the absence of infections, fever or other symptoms of systemic disease.[9]

In relapsing patients, the most common symptoms at onset are loss of power and/or sensation in one or more limbs, visual defects, or a combination of multiple symptoms.[1] In the early phase of MS, patients generally recover from relapses fully, without treatment, within days or weeks. However, over time, neurological deficits from relapses can accumulate, resulting in irreversible disability.[10]

In a minority of patients with subtle clinical progression at onset, symptoms may consist of gradual loss of power in the lower limbs, often accompanied by sensory disturbances and bladder/bowel dysfunction.[11] Symptoms progressively worsen over months or years, and patients are often unable to pinpoint the actual starting date.

In clinical practice, symptoms are generally investigated across different neurological systems:

- Visual (e.g. changes in visual acuity and/or visual field)
- Brainstem (e.g. nystagmus, diplopia, trigeminal neuralgia, dysarthria, dysphagia)
- Pyramidal (e.g. reduced power and mobility, spasticity)
- Cerebellar (e.g. tremor, ataxia, problems with balance)

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What are the management approaches?

- Sensory (e.g. changes in superficial, vibration or position sense, pain)
- Bowel/bladder (e.g. urinary urgency, urinary retention, bowel dysfunction, sexual dysfunction)
- Cerebral (e.g. changes in mentation, depression, fatigue)

Based on a combination of these systems, an overall disability level can be scored with the Expanded Disability Status Scale (EDSS), which uses an ordinal scale of increasing severity from 0 (absence of neurological symptoms and signs) to 10 (death related to MS), with 0.5 unit increments.[12] Generally, EDSS steps 1.0 to 3.5 indicate unrestricted walking, while EDSS steps 4.0 to 7.5 indicate progressive reduction in walking ability.[12]

The classification of MS phenotypes is shown in table 1, opposite. Following the first relapse, the condition is termed either clinically isolated syndrome (CIS) or relapsing-remitting MS (RRMS), depending on whether additional tests (e.g. MRI, CSF analysis) suggest dissemination in time (DIT) and space (DIS).[3,9,13]

On the occasion of a second clinical relapse, the condition inevitably falls within RRMS.[3,9,14] Following this initial relapsing-remitting course, patients can develop progressive disability, independently from relapses; this disease stage is named secondary progressive MS (SPMS).[13,15]

In around 10% of patients, a gradual worsening of disability can occur from the start of the disease, which is termed primary progressive MS (PPMS).[13]

Of note, patients diagnosed with PPMS and SPMS may also experience periods of symptom remission (and sometimes improvement), within an overall declining trajectory, and can still present with inflammatory activity (e.g. clinical relapses or evidence of MRI activity). As such, PPMS and SPMS have been reclassified as different parts of the same progressive spectrum, and more attention is actually given to the detection of clinical and/or MRI evidence of disease activity.[13,16]

DIAGNOSIS

A diagnosis of MS requires that clinical, radiological and laboratory signs of MS are disseminated in both time and space, as originally described in the 2001 McDonald criteria and subsequently revised in the 2017 Thompson revision (see table 2, opposite).[3,9,17,18] This revision has been specifically implemented in order to facilitate an earlier and more accurate diagnosis.[3,9,17,18] Overall, MS diagnosis is based on the combination of clinical features (relapses and clinical progression), MRI findings (T2 and T1 gadolinium-enhancing lesions in periventricular, cortical/juxtacortical, infratentorial and/or spinal cord areas), and CSF analysis (the presence of oligoclonal bands in the CSF indicates disseminated inflammatory activity within the central nervous system).[3]

Because of the variability of clinical presentation and the existence of different phenotypes, on the first assessment, frequently carried out in primary care, blood tests should be ordered to exclude any alternative diagnoses which may mimic MS symptoms. These include: full blood count, inflammatory markers (e.g. ESR, CRP), liver function, renal function, calcium, glucose, thyroid function, vitamin B_{12} and HIV serology.[19] Subsequently, if blood test results are within normal limits, a brain MRI without a contrast enhancing agent (gadolinium) is generally ordered.

Clinical history and MRI findings could be sufficient to make a diagnosis of MS in particular in the presence of lesions with topography and morphology typical of MS. If not, following neurology consultation, other tests could be considered, such as spinal cord MRI, repeated brain/spinal cord MRI with gadolinium, and/or CSF examination.

The incidental finding of MS-like lesions on brain MRI in individuals without any clinical history of neurological dysfunction is called radiological isolated syndrome (RIS).[7] RIS is seen by many as potentially the initial stage of MS.[20]

Referral to an MS team is helpful to confirm the MS-like nature of MRI findings and to exclude any subtle symptoms (e.g. defects in specific cognitive functions). Additional tests (e.g. CSF analysis, visual evoked potentials) can be considered to estimate the likelihood of future conversion to MS, though no specific treatment is currently indicated in RIS.

MANAGEMENT

Disease modifying treatments

MS is currently not curable. Disease modifying treatments (DMTs) can reduce the risk of new neurological symptoms, severe ambulatory impairment (EDSS 6.0), and death in people with RRMS, compared with no treatment or placebo.[21-23] As such, patients with MS undergo regular neurological consultations, blood tests, and MRI scans for disease and DMT monitoring.[1,4]

More than ten DMTs have been developed and approved for RRMS and CIS over the past 20 years, but only three for progressive MS (interferon beta 1b and siponimod for SPMS, and ocrelizumab for PPMS).[24-27] DMTs for RRMS and CIS mainly target inflammatory cells (e.g. lymphocytes) and mechanisms (e.g. cytokine production, CNS permeability to inflammatory cells); by contrast, to treat progression effectively, DMTs need to target neurodegeneration through neuroprotection and repair, which is much more challenging in light of the complexity of underpinning pathology.[28,29]

For each DMT, MS teams will recommend specific follow-up protocols including regular blood tests and MRI scans, to monitor both treatment response and side effects. Although follow-up and monitoring are generally carried out at MS clinics, patients may present to their GP with side effects from DMTs.

Most side effects are mild and easy to deal with (e.g. flu-like syndrome, gastrointestinal problems, flushing, injection site reaction, infusion-related reactions). However, some side effects are potentially life-threatening and need to be detected early and treated effectively.

Some DMTs increase the risk of infections (e.g. respiratory tract, urinary tract, herpes virus infections), while others can cause autoimmune diseases (e.g. immune thrombocytopenia, thyroid disease, kidney damage), requiring immediate diagnosis and treatment.

More recently, cardiovascular problems (e.g. myocardial ischaemia, myocardial infarction, cerebral haemorrhage, cervico-cephalic arterial dissection, pulmonary alveolar haemorrhage and thrombocytopenia) have been reported in alemtuzumab-treated patients, and the risk of progressive multifocal leukoencephalopathy (PML), a rare but potentially life-threatening disease of the CNS, caused by activation of the John Cunningham virus (JCV), has been extended from natalizumab to dimethyl fumarate and fingolimod.[24,25,30]

Treatment of relapses

Patients with established MS may consult their GP with new, acute onset neurological symptoms. First, the presence of infections (e.g. respiratory and urinary) should be ruled out, since they can cause disease worsening mimicking a neurological relapse.[31] Also, it is important to establish, before

referral to the MS team, that new symptoms (or worsening of existing symptoms) have persisted for more than 24 hours.

Treatment for relapses of MS should be offered if there is an impact on daily activities and, ideally, as early as possible, within 14 days from the onset of symptoms. Standard treatment is oral methylprednisolone 0.5 g daily for 5 days.[31] Of note, steroid treatment does not affect the overall outcome of the relapses and/or the long-term disease progression, but only shortens the time to recovery.[32] Thus, potential benefits should be carefully weighed in relation to risk (e.g. worsening of mental health conditions, hypertension, poor glucose »

Table 1

Classification of MS clinical phenotypes. Adapted from Lublin FD et al. Neurology 2014[14]

Phenotype classification for relapsing patients

CIS	Clinical relapses, and/or new/enlarging T2 lesions, and/or T1-enhancing lesions?	**Yes** Active **No** Not active	→	**Active CIS*** **Not active CIS**
RRMS	Clinical relapses, and/or new/enlarging T2 lesions, and/or T1-enhancing lesions?	**Yes** Active **No** Not active	→	**Active RRMS** **Not active RRMS**

*Active CIS is classified as RRMS

Phenotype classification for progressive patients

PPMS (from disease onset)	Clinical relapses, and/or new/enlarging T2 lesions, and/or T1-enhancing lesions?	**Yes** **No**	→ →	**Active and with progression** **Not active but with progression**
Progressive MS (after a relapsing phase)	Clinical progression on annual review?	**Yes** **No**	→ →	**Active but without progression** **Not active and without progression**

SPMS

CIS = clinically isolated syndrome RRMS = relapsing-remitting MS PPMS = primary progressive MS SPMS = secondary progressive MS

Table 2

2017 Thompson revisions of McDonald criteria for MS diagnosis. Adapted from Thompson AJ et al. Lancet Neurology 2018[3]

Clinical, radiological and laboratory criteria for MS diagnosis in different clinical presentations

Clinical presentation	2017 Thompson revision of McDonald criteria
≥2 relapses and objective clinical evidence of ≥2 lesions or of 1 lesion with reasonable historical evidence of a prior relapse	None
≥2 relapses and objective clinical evidence of 1 lesion	DIS demonstrated by: ≥1 T2 lesion in at least 2 of 4 MS-typical regions, or further relapse implicating a different CNS site
1 Relapse and objective clinical evidence of ≥2 lesions	DIT demonstrated by: simultaneous presence of T1-enhancing and T2 lesions, or a new T1-enhancing or T2 lesions on follow-up, or further relapse, or CSF-specific oligoclonal bands
1 Relapse and objective clinical evidence of 1 lesion (CIS)	● DIS demonstrated by: ≥1 T2 lesion in at least 2 of 4 MS-typical regions, or further relapse implicating a different CNS site ● DIT demonstrated by: simultaneous presence of T1-enhancing and T2 lesions, or a new T1-enhancing or T2 lesions on follow-up, or further relapse, or CSF-specific oligoclonal bands
Insidious neurological progression suggestive of MS (PPMS)	One-year disease progression and 2 of the following 3 criteria: ● ≥1 T2 lesions in periventricular, cortical/juxtacortical or infratentorial areas ● ≥ 2 T2 lesions in the spinal cord ● Positive CSF (CSF-specific oligoclonal bands)

key points

SELECTED BY

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Multiple sclerosis (MS) is the leading cause of non-traumatic neurological disability in young adults. Between 1990 and 2016, the UK prevalence increased by 28%, as a consequence of both earlier diagnosis and increased survival. The 2018 prevalence in England was estimated to be 190 cases per 100,000, with 105,800 affected individuals. The female to male ratio is 2:1, and patients have a minimally reduced life expectancy.

Diagnostic criteria require that clinical, radiological and laboratory signs of MS are disseminated in both time and space. Diagnosis is based on a combination of clinical features (relapses and clinical progression), MRI findings, and CSF analysis. When patients first present to primary care, blood tests should be ordered to exclude alternative diagnoses which may mimic MS symptoms. A full blood count, ESR, CRP, liver and renal function tests, calcium, glucose, thyroid function tests, vitamin B_{12} and HIV serology are recommended.

In most cases, clinical presentation is characterised by relapses. A relapse is defined as acute-subacute onset of neurological symptoms lasting at least 24 hours, in the absence of infections, fever or other symptoms of systemic disease. In relapsing patients, the most common symptoms at onset are loss of power and/or sensation in one or more limbs, visual defects, or a combination of multiple symptoms. In the early phase of MS, patients generally recover fully from relapses without treatment, within days or weeks. However, over time, neurological deficits from relapses can accumulate, resulting in irreversible disability. In the minority of patients with subtle clinical progression at onset, symptoms may consist of gradual loss of power in the lower limbs, often accompanied by sensory disturbances and bladder/bowel dysfunction.

When patients present to their GP with new, acute onset neurological symptoms, infection (particularly respiratory and urinary) should be ruled out, as infection can cause disease worsening and mimic a neurological relapse. It is important to establish, before referral to the MS team, that new symptoms (or worsening of existing symptoms) have persisted for more than 24 hours. Treatment for relapses of MS should be offered, as early as possible, if there is an impact on daily activities; standard treatment is oral methylprednisolone 0.5 g daily for 5 days.

Disease modifying treatments can reduce the risk of new neurological symptoms, severe ambulatory impairment and death in relapsing-remitting MS. Although follow-up and monitoring are generally carried out at MS clinics, GPs should be aware of potentially life-threatening side effects which need to be detected early and treated effectively. MS patients have high rates of comorbid depression, anxiety, cardiovascular disease, epilepsy, metabolic disease, and autoimmune diseases. A general health review (weight, smoking, access to routine health screening and care of other chronic conditions) should be carried out at least once a year.

control).[31] Ultimately, the MS team should be informed and more active DMTs considered.

Treatment of MS symptoms

Patients with MS require lifelong multidisciplinary management from a range of healthcare professionals (e.g. ophthalmology, urology, psychology, rehabilitation, occupational therapy, speech therapy),[1,4] though the first therapeutic approach is frequently carried out by GPs.

Among the most common symptoms, spasticity can be treated with baclofen or gabapentin as first-line drugs; alternatively, tizanidine, dantrolene or benzodiazepines can be considered. More recently, cannabis-based medicinal products have become available for adults with MS spasticity, though prescription is currently restricted to specialist clinics.[33] Referral to spasticity clinics should be considered in refractory cases.[19]

Pain can be treated as neuropathic pain (e.g. amitriptyline, duloxetine, gabapentin or pregabalin as initial treatment).[34]

Fatigue can be addressed with mindfulness-based training, cognitive behaviour therapy or fatigue management programmes, while pharmacological treatments (e.g. amantadine) are generally less effective.[19,35]

Similarly, in the absence of pharmacological treatments, problems with balance can be addressed by falls management programmes, balance rehabilitation and aquatic exercises.[35] Even in severely disabled patients, rehabilitation including a standing frame programme can be beneficial.[36]

COMORBIDITIES

Patients with MS should have their general health evaluated regularly, at least once a year, (e.g. weight, smoking, access to routine health screening, care of other chronic conditions),[31] all of which can directly and indirectly affect MS relapses and disability.[19,37-40]

Patients with MS have high rates of comorbid depression, anxiety, cardiovascular disease, epilepsy, metabolic diseases, and autoimmune diseases.[41-43] Overall, comorbidities have an adverse influence on MS outcomes and, thus, should be carefully evaluated and treated as in the general population.[44,45]

Vitamin D deficiency has been investigated as a possible determinant of MS risk and progression. To date, there is no evidence supporting the use of vitamin D as a treatment for MS.[46] However, GPs should refer to general recommendations for vitamin D supplements in specific populations at risk of deficiency, for instance MS patients with reduced mobility are inevitably less exposed to sun.[47]

CONCLUSIONS

GPs have a crucial role in seeing people presenting with new neurological symptoms suggestive of MS, and, following initial assessment, in referring them to specialised MS teams. Early diagnosis and treatment are vital to prevent irreversible disability accrual.

Once diagnosis has been established, GPs should work with the MS team within common management strategies and shared care. GPs have a key role in identifying so-called hidden symptoms of MS, especially those symptoms that may be hard to detect in neurology clinical practice but affect patients on a daily basis (e.g. fatigue, bladder and bowel problems, pain, cognitive dysfunction, depression and sexual dysfunction). GPs are at the frontline for the detection of new neurological symptoms and/or potential side effects of DMTs, and onward referral to different specialists to treat MS symptoms. Comorbidities should be carefully evaluated and treated, and a healthy lifestyle should be encouraged, bearing in mind its positive effects on MS.

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Useful information

MS Society
www.mssociety.org.uk

MS Trust
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NICE
www.nice.org.uk/guidance/conditions-and-diseases/neurological-conditions/multiple-sclerosis

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