Multiple sclerosis – an overview on epidemiology, pathogenesis and diagnosis

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Abstract
This overview will address the epidemiology, main risk factors and clinical course of multiple sclerosis (MS). The clinical as well as pathophysiological features of both relapsing–remitting and progressive MS will be discussed. Furthermore, an overview of diagnostic criteria will be given, supplemented by a differential diagnostic work-up for the clinician.

Epidemiology
Multiple sclerosis (MS) is one of the most common neurological diseases in young adults in Europe and North America, with around 2.5 million people worldwide affected by this chronic inflammatory disease of the central nervous system (CNS). MS has often been viewed as a ‘white man’s disease’ and, indeed, the disease is not evenly distributed across continents and ethnicities. One of the first systematic epidemiological studies, conducted by Davenport in 1922, described a higher frequency of MS in men drafted to the US army from northern states than from southern states, and noted the high risk in people of Scandinavian ancestry. Davenport suggested a latitudinal effect as well as a possible racial effect to account for this difference. One of the most comprehensive reviews of the distribution of MS in the second half of the twentieth century was conducted by Kurtzke. Kurtzke distinguished between high-risk regions (i.e. northern parts of Europe and North America), with prevalence rates of > 30 per 100000 population, and low-risk regions (i.e. southern parts of Europe and North America, and South America and Asia), with prevalence rates of <5 per 100000. Although incidence and prevalence data published in modern epidemiological studies are liable to stochastic variation, differences in diagnostic criteria, the inclusion of possible MS cases, ascertainment errors, selection bias and age and sex adjustment, the existence of continental differences is beyond controversy, with prevalence rates of up to 220 per 100000 population (median 108 per 100000) in Western Europe and up to 300 per 100000 (median 140 per 100000) in the USA. Corresponding prevalence rates in Asia, Africa and South America are <50 per 100000. Moreover, according to the Multiple Sclerosis International Federation’s Atlas of MS 2013, the global median prevalence of MS has increased from 30 per 100000 in 2008 to 33 per 100000 in 2013. A constantly increasing women-to-men ratio in patients with MS has been reported in recent decades in some studies but disputed in others.

Causes and risk factors
Disease susceptibility in MS seems to depend on a complex interplay between genetic and environmental risk factors. This view is supported by studies of twins: in genetically different, dizygotic twins the risk of developing the disease is around 5% in both siblings (compared with 0.1% in the general population). In contrast, in genetically identical, monozygotic twins, the probability is much higher, at around 30%. This difference underlines the importance of both genes and additional (environmental) factors in disease risk, as even in identical twins the disease concordance is far from complete. But which are the genes that contribute to MS predisposition? Clearly, there is no single ‘disease gene’ as there is in the case of monogenic diseases such as cystic fibrosis. Instead, there are many gene variants that can increase
(or decrease) disease risk. That predisposition to MS is linked to the human leucocyte antigen (HLA) gene complex, which encodes the major histocompatibility complex proteins and controls antigen recognition by T-lymphocytes, has been well established. Specifically, the HLA DR2 variant increases MS risk significantly, while another variant – HLA A2 – is protective. HLA genes are the strongest risk genes, but they are not the only ones. Recent genome-wide association studies have identified more than 150 MS-associated gene variants outside the HLA gene complex. Interestingly, most of these genes encode or regulate structure and functions of the immune system, lending further support to the immune concept of MS.

More than 50 environmental risk factors with a possible association to MS have been studied in recent years, including Epstein–Barr virus (EBV), human herpesvirus type 6, mycoplasma pneumonia, vaccination, smoking, vitamin D deficiency, exposure to ultraviolet radiation, diet, traumatic events, surgery, exposure to environmental agents and comorbid diseases. Infectious agents have attracted particular attention, as foreign agents may have a nuclear antigen that is structurally homologous with myelin sheet components such as myelin basic protein (MBP) or myelin-associated glycoprotein. Thus, when immune cells are activated by such pathogens, ‘collateral’ damage to the myelin sheet could occur.

Smoking is another putative environmental factor, as it produces nitric oxide and carbon monoxide, both of which are critical players in lipid peroxidation and mitochondrial damage, leading to oligodendrocyte apoptosis, axonal degeneration and demyelination.

Vitamin D deficiency is also discussed as an environmental risk factor, as its metabolism is dependent on ultraviolet B radiation and the prevalence and incidence of MS are dramatically lower in areas with high sun exposure. Vitamin D plays an important role in cell proliferation and differentiation as well as gene expression and regulation of immunity, thus probably influencing the origin and course of MS.

However, to date there is no robust evidence about a particular environmental factor in the pathogenesis of MS, as most studies in this field include caveats that cast doubt on their validity. A recent meta-analysis found only immunoglobulin G antibodies to EBV, a history of infectious mononucleosis and smoking to have a consistent association with the appearance of MS.

**Pathogenesis**

According to the currently prevailing pathogenic concept of MS as an inflammatory disease, MS is caused by an autoimmune attack, primarily directed against the myelin sheet of CNS neurons. T-cells with receptors for myelin determinant are regular components of the healthy immune repertoire. On pathological activation, these cells cross the blood–brain barrier (BBB), enter the CNS parenchyma and trigger a cascade of events that culminate in the histological hallmark of an active MS lesion, including infiltrations of T-cells, macrophages and B-cells; degradation of myelin and, to a lesser extent, axons; and reactive changes in astrocytes and microglia. Autoimmune T-cells recognize ‘their’ autoantigen presented on local antigen-presenting cells and become activated. They secrete proinflammatory mediators, which may act on neurons directly but, more importantly, recruit and activate accessory macrophages. Macrophages have an important role in creating acute neuronal dysfunction. First, they attack myelin sheaths and myelin-forming oligodendrocytes and, hence, are responsible for demyelination. Second, they can attack the denuded axons, causing direct disruption and indirect neuronal degeneration. T-cells also interact as helper cells with autoimmune B-lymphocytes, which produce myelin-specific autoantibodies. Certain autoantibodies bind to the surface of myelin sheaths and destroy them together with complement and/or macrophages.

This autoimmune concept is based on investigations using human CNS samples, mainly post mortem, and experimental animal models. The fact that only atypical MS cases undergo brain biopsy or postmortem analysis at early disease stages, as well as the fact that animal models can reproduce only in part disease processes in humans, have raised some concerns about this concept of MS.

Other, perhaps less likely, possibilities are that the inflammatory reaction is primarily directed against an unknown infectious agent, or that the inflammatory changes are secondary to a primary degenerative
process. These two fundamentally different concepts precipitate two different hypotheses.

According to the outside-in hypothesis, activated T-lymphocytes from the peripheral blood pass the BBB and cause focal inflammation within the CNS. Subsequently, inflammation is driven not only by T-lymphocytes but also by B-lymphocytes, macrophages and microglia, leading to focal demyelination as the histological hallmark of the disease, with relapses evident both radiologically – T2 lesions revealed by magnetic resonance imaging (MRI) – and clinically. After cessation of the inflammation, patients can be clinically stable for months or years until a new wave of T-lymphocytes invade the CNS, culminating in the next clinical attack. The outside-in hypothesis is strongly supported by the fact that all effective immunomodulatory treatments thus far act mainly on the peripheral immune system. In addition, it has been observed that the transfusion of purified, activated MBP-specific CD4 T-cells into healthy syngeneic animals can induce experimental autoimmune encephalomyelitis (EAE) – ‘transfer EAE’ – in recipients with clinical similarities to MS. This supports the hypothesis that there is an inflammatory component to the disease. On the other hand, no antigen has been identified to date that causes this peripheral immune activation with subsequent influx of inflammatory cells into the CNS.

The inside-out hypothesis argues that a primary CNS trigger (infection, metabolic defect) initiates a secondary immune cascade, leading to histologically confirmed inflammatory CNS lesions. Patients with cortical atrophy preceding demyelinating lesions and (rare) histologically confirmed cases of early MS without lymphocyte infiltrates within the CNS would support this hypothesis. However, similar to an ‘MS antigen’, a key defect in the CNS that could give rise to a subsequent inflammatory cascade has yet to be identified.

Despite these two fundamentally different hypotheses, convincing evidence exists to support the concept that MS is an autoimmune disease in which inflammatory demyelinating processes in early stages of the disease trigger a cascade of events that lead to subsequent neurodegeneration and that are amplified by pathogenic mechanisms related to brain ageing and accumulated disease burden. The later course of the disease, with its clinical counterpart of a secondary progressive course, is characterized by change in the inflammatory repertoire. Waves of inflammatory events driven by lymphocytes constantly decrease in frequency and intensity. At the same time, the inflammation is trapped behind an increasingly closed BBB. This leads to more diffuse inflammatory activity that most probably emerges from subpial meningeal B-cell follicles and mainly affects the grey matter of the brain with diffuse axonal damage and neurodegeneration, leading to diffuse brain atrophy. Although inflammatory components dominate the early phase of the disease, later stages are characterized by microglia activation, chronic oxidative injury, accumulation of mitochondrial damage in axons and age-related iron accumulation in the brain. Altered mitochondrial function in axons might be of particular importance. This process leads to chronic cell stress and imbalance of ionic homoeostasis, resulting in axonal and neuronal death.

Clinical presentation

The onset of the disease peaks at around the age of 30 years, with an age at onset of <20 years in around 10% of patients and >40 years in around 20% of patients. The disease shows female predominance, apparent in all representative studies, with sex ratios (female to male) of up to 3:1.

About 85% of MS patients initially present with relapsing–remitting MS (RRMS). In the majority of cases, this converts over time to secondary chronic progressive MS (SPMS) after a median of 15–20 years. Some patients, particularly directly after the transition from RRMS to SPMS, still have (so-called ‘superimposed’) relapses. About 15% of cases present with a primary progressive MS disease course. A small percentage of these patients have a progressive relapsing MS disease course. The clinical hallmark of RRMS is the relapse, defined as new symptoms or an aggravation of pre-existing symptoms that last >24 hours. The most common clinical symptoms associated with the initial relapse are weakness in one or more limbs, optic neuritis, paraesthesia, diplopia, vertigo and bladder dysfunction. With longer disease duration, gait disturbances, chronic fatigue, cognitive decline, pain, bowel and bladder disturbances and sexual
dysfunction become more prominent clinical features.

**Diagnosis and diagnostic criteria**

The diagnostic process has been summarized with the so-called McDonald criteria. These have been amended multiple times, with the latest refinement in 2010, and another amendment is expected in late 2017 or early 2018.

The diagnostic hallmark of the disease is the patient’s clinical presentation, with typical signs and symptoms related to demyelinating lesions, usually accompanied by imaging that is consistent with MS, disseminated in both space and time. At the same time, there should not be a better explanation for the symptoms, stressing the need for careful examination for a possible or probable alternative disease process.

Dissemination in space (DIS) refers to the requirement that lesions affect at least two areas of the CNS typically affected by MS. This can be demonstrated clinically, such as in a patient with a prior history of optic neuritis who now presents with a brainstem syndrome. In this case, DIS is satisfied if there is objective clinical evidence of these two separate lesions or if there is objective clinical evidence of one lesion with a reasonable historical account of the other. However, often a patient will present after only a single event, which is termed a clinically isolated syndrome (CIS). In this case, DIS may be satisfied if the clinician detects on neurological examination evidence for another separate lesion; however, DIS may also be satisfied with clinical evidence for only one lesion by incorporating the patient’s MRI data. MRI criteria for DIS require the presence of at least one T2 lesion in at least two of the four areas of the CNS typically affected by MS: periventricular, juxtacortical, infratentorial and spinal cord areas. If the patient has a brainstem or spinal cord syndrome, the symptomatic lesion has presumably already been ‘counted’ and, therefore, does not count towards the MRI criteria for DIS.

Dissemination in time (DIT) refers to the requirement that CNS lesions have developed over time, reducing the misdiagnosis of monophasic illness as MS. DIT can easily be clinically satisfied in a patient with two clinical attacks, again with objective clinical evidence for both attacks or for one with a reasonable historical account of the other. However, DIT can also be satisfied with a single clinical episode by the application of MRI criteria. With the patient’s initial MRI results, DIT can be satisfied by demonstration of the presence of both gadolinium-enhancing and non-enhancing lesions on the same scan, as this illustrates that the lesions presumably developed at different points in time. However, the enhancing lesion may not be the symptomatic lesion, which has already been counted. In addition, DIT may be satisfied by the development of any new T2 and/or gadolinium-enhancing lesions with reference to the baseline scan, regardless of the time interval between them.

Cerebrospinal fluid analysis is no longer a requirement for the diagnosis of RRMS according to the McDonald criteria. However, it is recommended as an additional diagnostic step to increase the rate of correct diagnosis, particularly after a patient’s very first clinical attack and in cases in which diagnosis is not entirely clear.

The category CIS was recently added to the McDonald classification scheme, although the term has been used for many years in both research and clinical practice. CIS represents a patient’s initial presentation with clinical symptoms typical of a demyelinating event. A patient is classified as having CIS when there is clinical evidence of a single exacerbation and the MRI results do not fully meet RRMS criteria. From a practical standpoint, there is little difference in approach for a patient with CIS and a patient with RRMS as multiple studies have now demonstrated that patients with a typical CIS, especially those with brain lesions consistent with MS as established by MRI, have a high likelihood of going on to meet RRMS criteria in the future and early treatment is effective at preventing additional relapses.

As the use of MRI has become increasingly widespread in cases of headache, trauma and other conditions, abnormalities suggestive of MS have been noted in patients who have not previously experienced clinical symptoms of the disease. The term radiologically isolated syndrome (RIS) was introduced in 2009 and requires that lesions are ovoid and well circumscribed, are not consistent with a vascular pattern and meet three out of four Barkhof criteria: one gadolinium-enhancing lesion or at least nine total T2 lesions, one juxtacortical lesion, one infratentorial lesion and three periventricular lesions. The findings must be
incidental, meaning that there must be no history of neurological symptoms suggestive of a demyelinating event and the lesions must not account for functional impairment. The risk of converting from RIS to a first clinical symptom suggestive of MS was 34% after a mean follow-up of 4.4 years. Younger age, male sex and the presence of spinal cord lesions were predictive of a conversion to CIS.

**Differential diagnosis**

Multiple sclerosis still relies on clinical diagnosis as no specific biomarker for the disease has been identified. Diagnosis depends on appropriate interpretation of MRI data in patients with the appropriate history and neurological examination suggestive of demyelination. Despite well-validated diagnostic criteria, misdiagnosis remains a significant problem, with implications for patients, their providers and health-care systems. In a recent multicentre study of 110 misdiagnosed patients, 22% suffered from migraine alone or in combination with other diagnoses, 15% from fibromyalgia, 12% from non-specific or non-localizing neurological symptoms with abnormal MRI results, 11% from conversion or psychogenic disorders and 6% from neuromyelitis optica spectrum disorder. Duration of misdiagnosis was ≥10 years in 33% of patients. A total of 70% of misdiagnosed patients received disease-modifying therapy, with 31% experiencing unnecessary morbidity due to misdiagnosis and incorrect treatment.

The differential diagnosis of MS should include other demyelinating syndromes, diseases typically causing multiple lesions in the brain and often following a relapsing–remitting course, isolated or monophasic syndromes, systematized diseases with symmetrical manifestation and a progressive course, and non-organic symptoms.

Common diseases that should be incorporated in an accurate diagnostic work-up are listed below.

**Other demyelinating syndromes**

- Isolated demyelinating syndromes
  - optic neuritis
  - spinal cord lesions
  - acute necrotizing myelitis
  - transverse myelitis
  - chronic progressive myelopathy
  - radiation myelopathy
  - HTLV-1-associated myelopathy.
- Multiple sclerosis variants
  - Marburg variant
  - Baló’s concentric sclerosis.
- Neuromyelitis optica and neuromyelitis optica spectrum disorders.
- Myelin oligodendrocyte glycoprotein-associated syndromes.
- Leucodystrophies
  - adrenoleukodystrophy
  - metachromatic leucodystrophy
  - Krabbe disease
  - Canavan disease
  - Alexander disease
  - Pelizaeus–Merzbacher disease
  - vanishing white matter disease
  - oculodentodigital syndrome.
- Central pontine myelinolysis.

**Diseases causing multiple lesions with possible relapsing–remitting course**

- Acute disseminated encephalomyelitis
  - relapsing ADEM
  - autoimmune encephalitis
  - paraneoplastic encephalitis
  - acute haemorrhagic encephalomyelitis
  - post-vaccination encephalomyelitis.
- Systemic lupus erythematosus.
- Antiphospholipid antibody syndrome.
- Primary Sjögren syndrome.
- Behçet’s disease.
- Central nervous system vasculitis.
- Non-inflammatory vascular disorders.
- Sarcoidosis.
- Chronic infections
  - Lyme disease
  - meningovascular syphilis
  - human immunodeficiency virus encephalitis
  - progressive multifocal leuencephalopathy
  - subacute sclerosing panencephalitis
  - Whipple disease.
- Central nervous system lymphoma.
- Mitochondrial diseases.
Systematized CNS diseases

- Hereditary ataxias and paraplegias.
- Leucodystrophies.
- Vitamin B₁₂ deficiency.
- Cerebrotendinous xanthomatosis.
- Phenylketonuria.
- Leuencephalopathy related to glue-sniffing.
- Multiple system atrophy.
- Paraneoplastic syndrome.
- Coeliac disease.
- Myeloneuropathy from acquired copper deficiency.
- Motor neuron disease and variants.

Isolated or monosymptomatic CNS syndromes

- Spinal cord
  - compression
  - cervical spondylotic myelopathy
  - Chiari malformation
  - spinal dural arteriovenous malformation
  - HTLV-1 myelopathy
  - primary lateral sclerosis
  - spinal cord stroke
  - transverse myelitis
  - other myelitides.

- Optic nerve
  - anterior ischaemic optic neuropathy
  - Leber's hereditary optic neuropathy
  - central serous retinopathy
  - neuroretinitis
  - chronic relapsing optic neuritis
  - paraneoplastic optic neuritis
  - amблиopia associated with tobacco or alcohol abuse.

Non-organic psychiatric diseases

Overall, a diagnosis of MS should be made only if the clinical history, neurological examination results and MRI results are consistent with MS, suggesting dissemination in space and time either clinically or radiologically. Moreover, there should not be a better explanation for the patient's presentation.

References


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State-of-the-Art Review

Immunomodulatory treatments for relapsing–remitting multiple sclerosis

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Abstract

Multiple sclerosis (MS) is an autoimmune disease of the central nervous system that encompasses both neuroinflammatory and prominent neurodegenerative aspects. A significant proportion of MS patients will develop neurological disability over time, and until recently, licensed drugs could not satisfactorily halt this process. However, in recent years, MS treatment has entered a phase of rapid progress. Several new drugs with significantly improved efficacy have entered the therapeutic field, and several others are currently undergoing phase III clinical trials. In this review, the efficacy data and safety and tolerability issues of currently licensed drugs for relapsing–remitting MS will be summarized, including a short update on new drugs currently undergoing late-stage clinical trials.

Introduction

For most of the time since the first description of a (possible) case of multiple sclerosis (MS) in the fourteenth century,1 treatment was restricted to prayer, medical spa, silver iodide, mercury and blood-letting. It was 500 years before the first anti-inflammatory treatments, corticosteroids and azathioprine, became available in the 1950s.

Another milestone was the introduction of interferon (IFN)β-1b (Betaseron®/Betaferon®, Schering) in 1993 after completion of the first large double-blind placebo-controlled study in patients with relapsing–remitting MS (RRMS).2 In the same decade, glatiramer acetate (GA) (Copaxone®, Biogen Idec) and two IFNβ-1a preparations (Avonex®, Biogen Idec; and Rebif®, Merck) were also licensed.3–5

Although these disease-modifying treatments were only moderately effective, they were widely used in clinical practice, most probably because of a lack of competitors. This situation changed with the emergence of the first monoclonal antibody (mAb): natalizumab (Tysabri®, Biogen Idec). Natalizumab was able to reduce the annualized relapse rate (ARR) by almost 70%, an improvement on the 30% ARR reduction of IFNs and GA. These promising results gave impetus to the development of several other mAbs such as ocrelizumab (Ocrevus®, Roche), alemtuzumab (Lemtrada®, Sanofi Genzyme) and daclizumab (Zinbryta®, Biogen Idec).

In addition to safety issues, mAbs have to be administered by injection, which has led to the development of more convenient oral formulations such as fingolimod (Gilenya®, Novartis), teriflunomide (Aubagio®, Sanofi Genzyme), dimethyl fumaride (DMF) (Tecfidera®, Biogen Idec) and cladribine (Mavenclad®, Merck).

This review will give an overview of established drugs and their upcoming novelties, with special emphasis on efficacy and safety issues. Our attention will focus especially on both recently approved drugs and some promising drugs producing positive results in phase III clinical trials.

Therapies for mild/moderate relapsing–remitting multiple sclerosis

Interferon β-1a, interferon β-1b and pegylated interferon β-1a

Mode of action

A multitude of mechanisms have been proposed to account for the anti-inflammatory and immunomodulatory capacity of the different IFNβ
preparations, although their in vivo relevance is still controversial. According to a recent review, the most relevant modes of action of IFNβ preparations in MS are (1) impairment of lymphocyte egress from the lymph node by up-regulating transcription of intracellular CD69, which selectively binds to sphingosine-1-phosphate (S1P) receptor 1 (S1P1), thus precluding its surface expression; (2) diminished ability of activated lymphocytes to cross the blood–brain barrier (BBB) by downsizing the density of adhesion molecules such as VLA-4 on their surface (while also mediating cleavage of the vascular cell adhesion molecule (VCAM) expressed on the surface of BBB endothelial cells to generate soluble VCAM); (3) directly increased expression and concentration of anti-inflammatory agents (Th2 pathway) and down-regulation of the expression of proinflammatory cytokines of the Th1 phenotype; (4) increased numbers of CD56bright natural killer (NK) cells in the peripheral blood; and (5) down-regulation of MHC class II mRNA, which limits the competence and availability of antigen-presenting cells.

Efficacy

Each of the three IFNβ preparations were licensed following a single multicentre double-blind placebo-controlled phase III trial: (1) IFNβ-1b subcutaneously every other day, (2) IFNβ-1a (Avonex) intramuscularly once weekly and (3) IFNβ-1a (Rebif) subcutaneously three times weekly. Although a recent Cochrane Review points towards a somewhat higher efficacy rate with higher dosage and higher administration frequency, a mean reduction in ARR and disability progression of around 30% over a 2-year period can be generally estimated.

Subsequently, IFNβ preparations were studied in patients with clinically isolated syndrome (CIS) and were shown to reduce the risk of conversion to clinically definite MS in this population, with the number needed to treat between 5 and 7. This positive effect was still evident at follow-up after 8 years. These results gave rise to a shift in the clinical paradigm, treating MS at earlier disease stages.

Although IFNβ preparations have satisfactory efficacy numbers together with a favourable long-term safety profile, their use is likely to peak and decline because the route and frequency of administration limit their patient convenience. This disadvantage was largely overcome with the introduction of pegylated IFN (PEG-IFN)β-1a (Plegridy®, Biogen Idec).

Pegylation of IFN means that at least one molecule of polyethylene glycol (PEG) is covalently added. This modification is a standard procedure to increase the stability, solubility, half-life and efficacy of a drug and is applied to several drugs and diseases. A global phase III clinical (ADVANCE) study investigated the efficacy of PEG-IFNβ-1a every 2 weeks in reducing the relapse rate in patients with RRMS. Compared with placebo, the ARR was reduced by about one-third, and the number of new or newly enlarging T2 brain lesions was reduced by two-thirds. Chronic administration of pegylated proteins, mostly at toxic concentrations, causes vacuolation of renal epithelium in animals, which – along with the occurrence of anti-PEG antibodies – needs to be addressed by phase IV studies.

Safety and tolerability

The most common side-effects reported in phase III trials and post-marketing surveillance include flu-like symptoms, abnormal liver function tests and injection-site reactions. Rare cases of severe hepatic injury, depression and thyroid gland disorders have also been reported. However, more importantly, a global safety database that has been accumulated over 15 years in the post-marketing period for intramuscular IFNβ-1a showed no malignancy risk. Glatiramer acetate and glatirameroids

Mode of action

Glatiramer acetate, composed of four amino acids (L-glutamic acid, L-alanine, L-lysine and L-tyrosine), was initially developed to mimic myelin basic protein (MBP) in order to induce experimental autoimmune encephalomyelitis (EAE). However, GA unexpectedly inhibited EAE in both rodents and monkeys and was developed as an immunomodulatory treatment for MS.

Similar to IFNβ, a multitude of mechanisms have been proposed to account for GA’s efficacy in treating RRMS: GA (1) shifts the T cell repertoire from an inflammatory Th1 towards an anti-inflammatory Th2 phenotype; (2) inhibits myelin reactive T-cells; (3) enhances the suppressor activity of CD8+ T-cells towards CD4+ T-cells; (4) may exert neuroprotective effects by stimulating T-cells to produce brain-derived neurotrophic factor (BDNF); and (5) affects B-cells by modulating their cytokine pattern and altering the expression of CD80, CD86 and MHC II, which in turn affects co-stimulatory signals required by T-cells in the inflammatory cascade.
Efficacy

Glatiramer acetate was licensed following a single multicentre randomized placebo-controlled trial. After 2 years, the drug showed a 29% reduction in ARR compared with placebo and a significant increase in the proportion of patients with an improved Expanded Disability Status Scale (EDSS) score.4 Although magnetic resonance imaging (MRI) measures were not included in the initial study, a subsequent multicentre double-blind placebo-controlled trial used MRI parameters as primary outcome parameters and showed a statistically significant difference in the number of gadolinium (Gd)-enhancing lesions, total T2 lesion volume and number of new T2 lesions between GA and placebo.9

Because high injection frequency and common local injection-site reactions are major confounders of convenience, and because they influence patients’ compliance negatively, a reduced dosing regimen has been investigated. A randomized double-blind placebo-controlled study16 was performed with >1500 patients receiving either 40μg of GA three times per week or placebo. The treatment group showed a 34.0% reduction in ARR and a 44.8% reduction in Gd-enhancing lesions or a 34.7% reduction in new or newly enhancing lesions. A dose of 40μg of GA was safe and well tolerated. The most common adverse events (AEs) in the GA group were injection-site reactions.

Safety and tolerability

The most commonly reported AEs in patients receiving long-term GA included local injection-site reactions (e.g. erythema, pain, nodules and oedema) and symptoms associated with an immediate post-injection reaction, which include vasodilation, chest pain, palpitation, tachycardia and dyspnoea. Observational studies covering a period of up to 15 years did not show an increased risk of malignancies, haematological abnormalities and renal or hepatic failure.17

Teriflunomide

Mode of action

Teriflunomide inhibits dihydroorotate dehydrogenase (DHODH) – the rate-limiting mitochondrial enzyme in de novo pyrimidine synthesis – by non-competitively antagonizing the binding of its substrate, dihydroorotate, and also competing with the binding of ubiquinone.18 Fast-proliferating lymphocytes are completely dependent on this enzyme to satisfy their pyrimidine need, whereas resting lymphocytes can use a salvage pathway to recruit pyrimidine independent of DHODH. Therefore, it is argued that teriflunomide acts as a selective immunomodulator rather than an immunosuppressant.19

Additionally, teriflunomide may impair the migratory capacity of T-cells, shift the T-cell phenotype from a proinflammatory Th1 to an anti-inflammatory Th2 pattern, decrease T-cell-dependent antibody (Ab) production and modulate the expression of adhesion molecules on neutrophils and macrophages.16 In vitro experiments also suggest a possible neuroprotective effect by suppressing astrocytic inducible nitric oxide (NO) synthase-mediated NO production.20 However, in vivo evidence of this effect is still lacking and, for now, its clinical meaning remains uncertain.

Efficacy

The first randomized double-blind placebo-controlled phase III trial – the Teriflunomide Multiple Sclerosis Oral (TEMSO) trial21 – compared two different doses of teriflunomide (7mg and 14mg) with placebo for 2 years in 1088 RRMS patients. Both doses reached the primary end point by significantly reducing ARR by 31%. However, a significant reduction in the rate of disability progression compared with placebo (by around 30%) was found only for the 14-mg group. Both dosing regimens also significantly influenced several MRI parameters to an extent that was similar to the currently available first-line immunomodulatory drugs used for MS.

The second randomized double-blind placebo-controlled phase III trial – the Teriflunomide Oral in People With Relapsing–Remitting Multiple Sclerosis (TOWER) trial22 – compared the same two doses with placebo in 1169 patients, with an average treatment duration of 18 months. Patients receiving 14mg had a 36.3% reduction in ARR and a 31.5% reduction in 12 weeks sustained disability progression, both results meeting statistical significance. The 7-mg
group also showed a 22.3% significant reduction in ARR, whereas there was no difference in the accrual of disability compared with placebo.

A third randomized double-blind placebo-controlled phase III trial—the Teriflunomide versus Rebif (TENERE) trial—used 44 mg of IFNβ-1a (Rebif) thrice daily as an active comparator to 7 mg and 14 mg of teriflunomide in 324 RRMS patients. The primary outcome parameter was time to treatment failure and was defined as either a further clinical relapse or trial withdrawal for any reason. No statistical difference was found between the three groups. ARR were comparable between the IFNβ-1a group and patients randomized to 14 mg of teriflunomide.

A once-daily dose of 14 mg of teriflunomide was approved by the FDA in September 2012 and by the European Medicines Agency (EMA) in August 2013 for patients with RRMS.

**Safety and tolerability**

Although teriflunomide is a new drug for MS, significant data on the safety profile of the drug can be deduced from leflunomide, which was licensed by the FDA in 1998 for RA. The safety profile and side-effect profile of leflunomide do not seem to be substantially different from data derived for teriflunomide in phase II and III clinical trials.

Common AEs are predominantly gastrointestinal (and include abdominal pain, diarrhoea, dyspepsia, nausea, vomiting, oral ulcers and elevated liver enzymes). The incidence and severity of most of these are dose dependent. Furthermore, alopecia, skin rashes and hypertension are described in a significant proportion of patients. The incidence of diarrhoea, nausea, alopecia and elevated liver enzymes are dose related. In the phase II extension study, the safety profile was favourable overall, although the discontinuation rate was 42%, and 19% of the total number of patients were linked to treatment-related (non-severe) AEs.

The incidence of serious AEs (SAEs) in the clinical trial programme of teriflunomide did not differ between the placebo and the 14-mg groups in terms of deaths, severe or opportunistic infections and malignancy. SAEs in leflunomide-treated patients included elevated liver enzymes, neutropenia, rare cases of interstitial lung disease and two cases of interstitial progressive multifocal leucoencephalopathy (PML). As these patients had a history of previous immunosuppression, no definite conclusions on the PML incidence risk of teriflunomide can be drawn.

Teratogenicity has been described in animal models, but reproductive toxicity data in humans are limited. Nevertheless, patients need to be made aware of the theoretical risk of teratogenicity based on animal data, and it is strictly required that pregnancy is excluded before initiation of teriflunomide treatment. Women must use effective contraception throughout the whole treatment period and for up to 1 year thereafter, as teriflunomide exerts long-lasting biological effects. Men are similarly cautioned to avoid fathering a child while on therapy. It is strongly advised that women who become pregnant during treatment use colestyramine (8 g three times a day for 11 days) as a washout procedure, which results in elimination rates of 90% at day 10. Breastfeeding is also not recommended for patients on teriflunomide.

**Future prospects**

In the Oral Teriflunomide for Patients with a First Clinical Episode Suggestive of Multiple Sclerosis (TOPIC) trial, both 7 mg and 14 mg teriflunomide significantly reduced the risk of conversion of CIS to clinically definite RRMS compared with placebo. Nevertheless, the licensing of teriflunomide for patients after a first clinical symptom suggestive of MS is still pending.

**Dimethyl fumarate**

**Mode of action**

Dimethyl fumarate ester compounds are licensed in several countries around the world to treat patients with severe psoriasis, and during the last 15 years they have proven to be a safe and relatively convenient drug for this purpose. A direct comparison with its use in MS is hampered by different dosage regimens: DMF is used only periodically in psoriasis, whereas it is used for many years without treatment holidays in MS.

The use of DMF overcomes the problem of poor absorption rates of fumaric acid after ingestion. Potential ulcerogenic side-effects of these esters necessitate the use of enteric-coated formulations. After gastric passage, DMF is almost completely absorbed in the small intestine and hydrolysed to monomethylfumarate (MMF), the biologically active metabolite.
Although the exact mode of action is poorly understood, two main mechanisms of the drug seem to be responsible for its clinical effect in MS:

1 DMF exerts anti-inflammatory effects on the immune system by (1) polarizing the immune system from a Th1 phenotype towards a Th2 phenotype, thus increasing the amount of anti-inflammatory cytokines compared with proinflammatory cytokines such as TNFα, interleukin (IL) 1β and IL-6; (2) preventing the nuclear translocation of cytoplasmic nuclear factor kappa B (NF-κB) and hence the NF-κB-driven transcription of proinflammatory cytokines; and (3) attenuating lipopolysaccharide-induced production of proinflammatory mediators including TNFα, IL-1β, IL-6 and NO from astrocytes and microglia.

2 DMF exerts neuroprotective effects via activation of the NF-E2-related factor 2 (Nrf2) antioxidant pathway. DMF rescues neurons and glial cells in culture from oxidative stress-induced cell death by inducing Nrf2-mediated dependent pathways, which induces phase 2 detoxifying enzymes [e.g. NAD(P)H]. Moreover, DMF can reduce T-cell migration via the BBB by inhibiting the expression of adhesion molecules on the surface of lymphocytes.

Efficacy

The Determination of the Efficacy and Safety of Oral Fumarate in Relapsing–Remitting MS (DEFINE) study randomized 1237 RRMS patients with at least one relapse in the prior 12 months to 240mg twice daily, 240mg three times daily or placebo for 96 weeks. ARR was significantly reduced in both treatment arms with a 53% reduction in the 240mg twice daily regimen. Twelve weeks sustained disability progression was also significantly reduced by 38% compared with placebo. In concordance with the clinical end points, DMF also showed statistically significant reductions in all relevant MRI parameters.

A second phase III trial – the Comparator and an Oral Fumarate in Relapsing–Remitting MS (CONFIRM) trial also randomized patients to receive one of two different DMF doses or placebo, and additionally added a GA group as a fourth treatment arm. However, the study was not sufficiently powered to detect a difference between DMF and GA, which prevented a direct comparison. Furthermore, there was no blinding to GA treatment. All active treatment arms showed a significant reduction in ARR, the primary outcome parameter of the study, with a more prominent reduction in the two DMF groups (44% in the 480-mg group and 51% in the 720-mg group vs. 29% in the GA group). There were also statistically significant reductions in the number of new or enlarging T2 lesions (by 71% and 54% vs. 73%, respectively) and the proportion of relapsing patients (34% and 29% vs. 45%, respectively). In contrast, the reduction in disability progression confirmed at 12 weeks showed no statistically relevant difference.

Based on the results of these two studies, DMF was approved for RRMS as Tecfidera – in doses of 240mg twice daily – by the FDA in May 2013 and by the EMA in January 2014.

Safety and tolerability

Adverse events occurring more frequently in DMF-treated patients in the phase II trials included gastrointestinal symptoms (nausea, diarrhoea and abdominal pain) and flushing, which typically occur within 30 minutes. The initial effect of MMF in enhancing TNFα would account for some of the AEs experienced in the initial period of DMF administration, especially flushing, diarrhoea and abdominal cramps. Other frequently reported side-effects include (dose-related) elevation of transaminase levels and lymphopenia. Lymphocyte counts decreased to 50% of baseline levels in up to 10% of patients within the first year of treatment. Nevertheless, in almost all patients, mean values remained within the normal range. Rare cases of proteinuria were described in both DEFINE and CONFIRM.

Although there was no difference in infection rates in the phase III trials, sporadic cases of PML have been reported with DMF compounds in the treatment of psoriasis, and with Tecfidera and other DMF compounds in MS. Older age and lower lymphocyte counts are discussed as probable risk factors for PML, although the overall low incidence precludes definite conclusions for now.

Future prospects

A phase III multicentre randomized double-blind assessment of DMF examining the time to a first attack in patients with radiologically isolated syndrome – the Assessment of Tecfidera in
Radiologically Isolated Syndrome (ARISE) study (NCT02739542) – is currently recruiting patients with incidental T2-hyperintense lesions suggestive of MS but without any clinical symptoms. The primary outcome parameter will be the time from randomization to the first demyelinating event (acute or development of an initial symptom resulting in a progressive clinical course). Results are expected in late 2020.

**Therapies for highly active relapsing–remitting multiple sclerosis**

**Natalizumab**

Mode of action

Natalizumab was the first mAb licensed for MS treatment. Natalizumab binds to the α4-integrin molecule, a component of VLA-4, on lymphocytes, thereby preventing binding to the ligand VCAM on endothelial surfaces. By this mechanism, the adhesion and subsequent migration of lymphocytes across the BBB is disabled, thus attenuating central nervous system (CNS) inflammation.

**Efficacy**

Two pivotal phase III trials led to the licensing of natalizumab by the FDA in 2004 and by the EMA in 2006 for the treatment of RRMS. The first pivotal trial – the Natalizumab Safety and Efficacy in Relapsing–Remitting MS (AFFIRM) trial – assigned 942 RRMS patients in a 2:1 ratio to receive either natalizumab (300mg) or placebo intravenously every 4 weeks for up to 116 weeks. Natalizumab reached the primary outcome parameter – reducing ARR by 68% compared with placebo – and secondary outcome measures, such as reducing sustained disability progression by 42% and MRI activity by up to 92%.

The second pivotal trial – the Safety and Efficacy of Natalizumab in Combination with IFNβ-1a in Patients with Relapsing–Remitting MS (SENTINEL) trial – randomly assigned 1171 patients who, despite IFNβ-1a treatment, had at least one relapse in the previous year. Patients were randomized to receive (in addition to IFNβ-1a) either 300mg of natalizumab or placebo as a monthly infusion. Compared with the IFNβ-1a+placebo group, the combination therapy offered a reduction of >50% in ARR and MRI activity, together with a reduction of 24% in sustained disability progression.

**Safety and tolerability**

In these pivotal trials, the only side-effects occurring more often in the natalizumab than in the placebo group were allergic reactions.

Following two cases of PML in the SENTINEL trial, natalizumab was voluntarily suspended by the manufacturer in 2005, but reintroduced in June 2006 with revised labelling and risk management programmes. As of August 2016, the overall incidence of PML in natalizumab-treated patients is 4.22 per 1000 patients. PML has been confirmed in 685 patients, of whom 77% are still alive with varying levels of disability. The duration of dosing prior to PML diagnosis ranged from 8 to 118 doses (Biogen, data on file). The most relevant risk factors are John Cunningham virus (JCV) exposure, indicated by the presence of anti-JCV Abs (anti-JCV Ab index), immunosuppressive treatment prior to natalizumab and longer treatment duration. Considering this, a more detailed risk stratification has been applied in recent years.

**Fingolimod**

Mode of action

Fingolimod, which is derived from myriocin, a metabolite of the fungus *Isaria sinclairi*, was the first orally available immunomodulatory drug to be licensed in Europe and the USA. In vivo, fingolimod is phosphorylated to fingolimod phosphate, which acts as a functional antagonist at most S1P receptors. S1P receptors are found on T-cells and mediate the egress of activated T-cells from lymphoid organs into the blood, thus preventing their infiltration into the CNS, a crucial step in the pathophysiology of MS. Moreover, S1P receptors are found on virtually all neural cell lineages and in vitro data suggest that fingolimod could affect oligodendrocyte precursor cell survival, recruitment, activation and astrogliosis. However, the evidence is not consistent and supporting *in vivo* data are lacking.

**Efficacy**

Data on clinical efficacy of fingolimod are mainly derived from two phase III trials. In the first trial – the FTY720 Research Evaluating Effects of Daily Oral Therapy in MS (FREEDOMS) trial – 1272 RRMS patients were randomized to receive 0.5mg or 1.25mg of fingolimod or placebo for 24 months. Both dosing regimens showed a significant reduction in ARR,
several MRI parameters and risk of disability progression compared with placebo. The second phase III trial – the Trial Assessing Injectable INF vs. FTY720 Oral in RRMS (TRANSFORMS) trial – tested whether or not fingolimod (either 0.5 mg or 1.25 mg daily) was superior to IFNβ1a in 1292 subjects over 12 months. Although fingolimod again showed a significant reduction in ARR (40%), the progression of disability over a 1-year period showed only a trend in favour of fingolimod. Therefore, fingolimod was approved by the FDA in October 2010 and by the EMA in March 2011 for patients with RRMS. However, the EMA restricted the use of fingolimod to patients with poor response to IFNβ or to therapy-naive patients with a severe disease course from onset.

Safety and tolerability

The most common side-effects of fingolimod (seen in >10% of patients) are flu infections, headache, cough, diarrhoea and back pain. Elevated liver enzymes (more than threefold the upper limit) were found in 9% and lymphopenia in 80% of patients. Less common side-effects include urinary tract infections, herpes infections (including rare cases of death due to herpes zoster virus infection), macula oedema and skin cancers. Rare cases of PML associated with fingolimod therapy have also been reported.

Cardiac AEs include mild hypertension, first-dose bradycardia reaching its maximum within 6 hours of first administration, and first- and second-degree atrioventricular conduction block. Because of several unexpected deaths and serious cardiovascular events, the labelling of fingolimod has been modified. The FDA and the EMA concluded that, overall, the benefits of the drug outweighed the risks and recommended that the drug not be prescribed to patients with pre-existing cardiac or cerebrovascular diseases or to those taking antiarrhythmics; however, if treatment was deemed necessary, a prior cardiological opinion was advised. Furthermore, obligatory monitoring for 6 hours during the first dose with baseline electrocardiography (ECG) became a requirement for all patients. Patients who develop a cardiac abnormality during the monitoring period should be admitted to hospital for overnight continuous ECG monitoring.

Future prospects

More selective S1P1 agonists are currently being tested in phase III clinical trials in RRMS with preliminary positive results for ponesimod (Actelion) and ozanimod (Celgene).

Alemtuzumab

Mode of action

Alemtuzumab is a humanized derivate of the Campath-1 series, initially manufactured to treat lymphocytic malignancies and subsequently developed for MS by the Cambridge group. Alemtuzumab is a humanized immunoglobulin G (IgG1) mAb directed against CD52: a small, 12-amino acid cell-surface protein abundantly expressed on B- and T-lymphocytes. To a small extent, CD52 is also expressed on monocytes, macrophages and NK cells with little or no expression on bone marrow stem cells, plasma cells and neutrophils. The biological role of CD52 is still unknown, but a role in T-lymphocyte migration and co-stimulation has been suggested. As CD52 knockout mice are phenotypically normal, CD52 may not be required for normal immune system function. Alemtuzumab produces a rapid (within 1 hour) and profound lymphopenia through two major mechanisms: Ab-dependent cellular cytolysis and complement-dependent cytolyis.

Cell repopulation kinetics vary between different lymphocyte subsets. Whereas median B-lymphocyte numbers reappear after 3–6 months, memory B-cells remain substantially depleted for up to 12 months. In the case of T-cells, repopulation lasts for up to 5 years, with reappearance more rapid for CD8+ cells than for CD4+ T cells. Moreover, the newly appearing lymphocytes seem to have a different phenotype. For example, the percentage of cells with a Treg phenotype (CD4+/CD25high, FoxP3 expression) was increased for up to 6 months after alemtuzumab treatment. In addition, when specifically stimulated with MBP, peripheral blood mononuclear cells cultured from alemtuzumab-treated patients produced increased concentrations of BDNF and ciliary neurotrophic factor, both rising during the 12 months post treatment and, therefore, suggesting a potential for enhancement of endogenous neural repair mechanisms.

Efficacy

Alemtuzumab has been used as an experimental treatment for MS in Cambridge since 1991. Although earlier studies in patients with secondary progressive MS (SPMS) showed a significant reduction in new Gd-enhancing lesions (GELs) on MRI and a reduction in the number of clinical relapses, patients still continued to accrue disability, and evidence of brain atrophy was demonstrated on MRI. This was in contrast to a cohort of relapsing patients, supporting...
the notion of a ‘window of opportunity’ with greater potential benefit from early immunotherapy in MS. As a result, the first randomized controlled phase II study comparing the effect of alemtuzumab with an established therapy of IFNβ-1a was performed, with a cohort of RRMS patients with a very short disease duration of ≤3 years and an EDSS score of ≤3.0. Patients randomized to alemtuzumab received intravenous cycles at a dose of either 12 or 24 mg per day on 5 consecutive days at month 0 and on 3 consecutive days at month 12. Both doses reduced ARR by 74% and risk of sustained disability progression by 71% compared with IFNβ-1a. Within the study period of 36 months, 80% of patients in the alemtuzumab group remained relapse free, compared with 52% in the IFNβ-1a group. Moreover, post hoc analysis revealed that a sustained improvement in disability was evident in 51.6% of alemtuzumab-treated patients compared with only 27.2% in the IFNβ-1a group. These data were confirmed in a 5-year follow-up study of the Campath-1H in MS (CAMMS223) cohort, with a reduction in risk of sustained disability accumulation of 72% and in risk of relapse of 69% compared with IFNβ-1a.

The first completed phase III trial – the Comparison of Alemtuzumab and Rebif Efficacy in MS (CARE-MS I) trial – was a 2-year trial with a similar design to CAMMS223 in comparing alemtuzumab to 44 μg of IFNβ-1a (Rebif) subcutaneously three times a week in 581 treatment-naive MS patients. In contrast to CAMMS223, only the 12-mg dose of alemtuzumab was used and a slightly longer disease duration of ≤5 years (compared with ≤3 years in CAMMS223) was eligible. The study reached the first of two co-primary outcomes with a 55% reduction in ARR at 2 years. However, the study failed to show superiority of 12 mg of alemtuzumab in reducing the number of patients with a sustained increase in the EDSS after 2 years (8% in the alemtuzumab group, compared with 11% in the IFNβ-1a group; P=0.22). Nevertheless, when compared with IFNβ-1a, alemtuzumab reduced the proportion of patients with GELs, new or enlarging T2 lesions and brain volume loss, each at a significant level.

The second phase III trial – the CARE-MS II trial – included 840 patients with a longer disease duration of ≤10 years who had experienced at least one relapse on previous standard immunomodulatory treatment. Similar to CAMMS 223, the study was initialized with two different alemtuzumab doses (12 and 24 mg), with the 24-mg arm prematurely stopped after enrolment of 164 patients because of safety concerns. Both primary outcome parameters were reached, with a reduction in ARR of 49% and a reduction in sustained disability progression at 24 months of 42% compared with IFNβ-1a. Moreover, 29% of the alemtuzumab group experienced a sustained reduction in disabilities compared with only 13% of the IFNβ-1a group. MRI parameters were also statistically significant for alemtuzumab, leading to a reduction in the number of patients with new or enlarging T2 lesions or GELs. Only the change in T2 hyperintense lesion volume from baseline to year 2 was not significant. The results of CAMMS223 and CARE MS I and II finally led to EMA approval in September 2013 for patients with active RRMS (defined by clinical or imaging features). The FDA postponed approval until 14 November 2014 owing to insufficient evidence that the benefits of alemtuzumab outweigh its SAEs.

Safety and tolerability

The safety profile derived from the CAMMS223 study has been confirmed by the later CARE-MS I and II studies, with the following key safety issues.

Infusion reactions occurred in >90% of patients, including SAEs in 3%. The most common infusion-related symptoms included rash, headache, pyrexia, nausea and flushing, all of which were related to acute cytokine release syndrome. The severity of these symptoms gradually decreased with the number of infusions received.

Infections occurred more often in the alemtuzumab group than in the INF group, with the most common infections being upper respiratory tract infections, urinary tract infections and herpes. Although increased numbers of herpes infections were noticed in CAREMS223 (8.3% in alemtuzumab-treated patients, compared with 2.8% in the IFNβ-1a-treated group), the high incidence of 16% in CARE-MS I and II led to a protocol amendment in 2009, determining that alemtuzumab-treated patients receive 200 mg of oral aciclovir twice daily during the infusion and for 28 days thereafter. This intervention decreased the frequency of herpetic infections from 3% to 1% following the second course of alemtuzumab in CARE-MS I, and from 2.8% to 0.5% in CARE-MS II.

Sporadic cases of malignancies were reported in the CAMM223 and CARE-MS I and II studies; however, there was no definite alert in terms of malignancy.
Autoimmune disorders continue to represent the major safety concern, with severe idiopathic thrombocytopenic purpura (ITP) and renal disorders being the more severe (but rare) AEs and thyroid disorders being the more common (but less severe) AEs. Severe ITP (including one death) was reported in CAMMS223 and CARE-MS I and II in a total of 16 patients treated with alemtuzumab, compared with only two patients receiving IFNβ-1a. One patient in CARE-MS I developed presumed autoimmune pancytopenia with fatal outcome; another patient developed glomerulonephritis. Outside clinical trials, other cases of Goodpasture syndrome have been reported in the Cambridge cohort.52

Thyroid disorders occurred in 18% of patients in the alemtuzumab group compared with 6% of patients in the IFNβ-1a group in CARE-MS I. Corresponding numbers in CARE-MS II were 16% and 19% (12 and 24mg) of patients in the alemtuzumab group compared with 5% in the placebo group. Hypo- as well as hyperthyroid gland disorders were reported; however, most were medically controlled, with surgical therapy required in only rare cases.

A long-term follow-up of 248 patients treated with alemtuzumab reported newly emerging autoimmune disorders in 22.2%, with thyroid gland disorders being the most common, at 15.7%. The incidence peaked after 12–18 months of treatment with no new cases identified 5 years after treatment initiation.53 The risk of autoimmunity is thought to be driven by higher levels of IL-21, raising the possibility that this could serve as a biomarker to identify patients at risk.43

**Daclizumab**

**Mode of action**

Daclizumab is a humanized mAb directed against the α-subunit of the high-affinity IL-2 receptor, sparing the low-affinity IL-2 receptor. The blockage of this receptor prevents activation, differentiation and proliferation while the number of CD56bright NK cells is increased.54 Daclizumab was originally approved by the FDA in 1997 to prevent acute kidney transplant rejections.

**Efficacy**

The efficacy of daclizumab was tested in two randomized double-blind placebo-controlled phase III clinical trials. In the first trial – the Daclizumab High-Yield Process in Relapse–Remitting Multiple Sclerosis (SELECT) trial55 – a monthly subcutaneous injection of 150mg of daclizumab showed a 54% reduction in ARR compared with placebo as the primary outcome parameter. At the same time, the secondary outcome parameter, confirmed disability progression, was also reduced by 56% compared with placebo. In the second trial – the Daclizumab HYP Versus Interferon β-1a in Relapsing Multiple Sclerosis (DECIDE) trial56 – daclizumab was compared with a standard treatment of IFNβ-1a once weekly. Again, daclizumab showed a significant reduction in ARR by 45%, while the secondary outcome parameter (reduction in confirmed disability progression) failed to reach statistical significance after 12 weeks.

Daclizumab was approved in 2016 by both the FDA and EMA for RRMS. However, its use was restricted by the EMA in 2017 to patients with highly active MS not controlled by other immunomodulatory treatments owing to safety concerns (fatal cases of liver injury).

**Safety and tolerability**

One of the most common side-effects of daclizumab is a (clinically asymptomatic) rise in liver enzymes, although rare cases of hepatic failure have been reported and finally led to restricted use in patients with otherwise uncontrolled disease activity. Moreover, monthly testing of liver enzymes during and 4 months after daclizumab therapy has been called for by the EMA.

Other side-effects include upper respiratory and urogenital tract infections, dermatological issues (rash, dermatitis, eczema) and gastrointestinal side-effects (diarrhoea). Moreover, physicians should carefully observe newly arising clinical signs of other autoimmune disorders, as rare cases of autoimmune hepatitis and thyroiditis have been reported.57

**Cladribine**

**Mode of action**

Cladribine is a purine analogon that blocks DNA synthesis in proliferating cells. The compound is a prodrug that is converted to its active form by deoxycytidine kinase. This enzyme is mainly active in lymphocytes, rather than in monocytes and other cell types of the human body, therefore leading to
a relatively specific suppression of activated T- and B-cells. Moreover, cladribine is a small molecule that can easily cross the BBB, resulting in speculation that it might also have beneficial effects within the CNS.

**Efficacy**

In a randomized double-blind placebo-controlled study – the CLAdRibin Tablets treating multiple sclerosis orally (CLARITY) study – cladribin showed a 57% reduction in ARR compared with placebo as well as a significant reduction in the proportion of patients with disability progression. Post hoc analysis showed a somewhat superior efficacy in patients with highly active RRMS, defined as patients with relapses despite immunomodulatory treatment or patients with at least two relapses in the previous year. In another randomized placebo-controlled trial, cladribine significantly reduced the risk of a second relapse and, consequently, the conversion to definite RRMS in patients with a CIS. The licensing of cladribine was initially postponed owing to safety concerns, but cladribine was approved in 2017 by both the FDA and EMA. Cladribine is taken orally for 4–5 days in week 1 and again in week 55. Thereafter, no further therapy is needed for at least 3 years. At present, there are only limited data on long-term therapy with cladribine.

**Safety and tolerability**

The most common side-effect of cladribine is lymphopenia. Therefore, white blood cell (WBC) counts should be taken before each treatment cycle and 2 and 6 months thereafter. In cases of lymphopenia, patients with WBC counts <5.0×10^9/l should be monitored closely. Neutropenia, thrombocytopenia and anaemia occur only in rare cases. As latent tuberculosis and hepatitis infections can be reactivated during cladribine therapy, these should be tested for and cladribine avoided in patients with active hepatitis, tuberculosis or human immunodeficiency virus (HIV) infection. Moreover, varicella zoster virus (VZV) vaccination should be considered for patients with negative VZV immunity. Although malignancies were more common in the cladribine group than in the placebo group of the CLARITY trial (which caused the initial postponement of the licensing of the drug), further analysis revealed that this was due to an uncommonly low malignancy rate in the placebo group.

**Mitoxantrone**

**Mode of action**

Mitoxantrone is a cytotoxic agent of the anthracenedione family that acts by intercalating with DNA and inhibiting topoisomerase II enzyme activity for DNA repair. It has immunosuppressive properties by reducing the number of B-cells, inhibiting T-helper cell function and augmenting T-cell suppressor activity. Having been widely used in the treatment of breast cancer and leukaemia, it has also been tested in patients with MS.

**Efficacy**

A phase II randomized controlled trial in 51 patients with RRMS showed a significant reduction in ARR and disability progression over 2 years with a monthly dosage of 8mg/m² over 12 months. A second trial recruited 42 patients with very active MS and randomized them to receive either 1g of methylprednisolone only or 1g of methylprednisolone in combination with 20mg of mitoxantrone monthly over 6 months. The combination therapy group showed a significant reduction in ARR and GELs as well as an improvement in mean EDSS scores at the end of the study.

Finally, the Mitoxantrone in MS (MIMS) study assigned a total of 194 patients with SPMS (with or without superimposed relapses) to receive 5mg/m² or 12mg/m² mitoxantrone or placebo every 3 months for a total of 2 years. Only patients receiving the higher dose showed a significantly reduced ARR and disability progression compared with placebo.

Based on these results, the FDA licensed mitoxantrone for use in MS in 2000. Mitoxantrone is also licensed for use in some European countries.

Different treatment regimens are used in different countries according to different regulatory demands. However, the two most common regimes used are 12mg/m² mitoxantrone intravenously every 3 months for 2 years (following the MIMS study) and 20mg of mitoxantrone intravenously and 1g of methylprednisolone every 4 weeks for 6 months.

**Safety and tolerability**

The most common side-effects of mitoxantrone include nausea, alopecia, increased risk of infections
and infertility. Post-marketing surveillance also raised concerns about cardioxicity and treatment-related acute leukaemia (TRAL) and resulted in a 2005 FDA ‘black box’ warning. A prospective registry on mitoxantone-related side-effects reported an incidence of congestive heart failure in 2% of patients and an incidence of TRAL in <1% of patients in a cohort of 509 US patients with a follow-up of 5 years.

Summary and conclusions

Major advances in the therapeutic landscape of MS have been achieved in the last 20 years. In the late 1990s only IFN and GA were available; now neurologists are able to choose from six different injectables with moderate efficacy but well-known safety profiles, four oral drugs with enhanced efficacy and satisfactory safety profiles and three antibodies with exceptional efficacy but challenging safety concerns. Moreover, many new treatment options for RRMS are on the horizon, some of them already in phase III clinical trials.

The encouraging development of therapeutic options has raised expectations, especially concerning efficacy of immunomodulatory drugs. In the 1990s, a 30% reduction in relapse rate was deemed to be satisfactory efficacy but, with the introduction of natalizumab into the therapeutic arena, freedom from disease activity became the sticking point in MS therapy, at least in a proportion of patients. However, with the increasing number of therapeutic regimens available, identifying the most appropriate drug for any individual patient will be a challenge of the near future. One of the main goals in the future will be to balance the efficacy and risk of any particular drug for individual patients.

Another goal, particularly when a heterogeneous disease such as MS is concerned, is to tailor available treatments to individual needs. Population-based genomics as a screening tool to stratify patients to certain drugs and dosage regimens is currently under investigation and has already proven useful in other neurological diseases. The feasibility of such strategies will increase as new-generation DNA-sequencing techniques rapidly become available and allow affordable analyses of whole genomes within weeks or days, accelerating the identification of genetic variants associated with the magnitude of response to a particular drug, as already practised in cancer therapy.66

References


STATE-OF-THE-ART REVIEW


Upcoming therapeutic options for progressive multiple sclerosis

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Abstract

Although a wide range of therapeutic options are available for relapsing–remitting multiple sclerosis (MS), the therapeutic landscape for progressive forms of the disease is highly unsatisfactory. Therefore, the identification of effective therapies for progressive MS (PMS) is a highly relevant challenge for the global MS medical community. To achieve this, a better understanding of the mechanisms involved in PMS is required through novel clinical trial designs, new drug repurposing strategies and new methods of collaboration in identifying effective therapies. In this review, we discuss the first compounds already available for PMS as well as other therapies currently undergoing phase II and III clinical trials.

Introduction

Although 13 immunomodulatory therapies are currently available for the treatment of relapsing–remitting multiple sclerosis (RRMS), the therapeutic arena for progressive multiple sclerosis (PMS) remains a no man’s land. This difference is driven, at least in part, by the factors presented below:

1 The mechanisms of PMS are less well understood than those of RRMS. The absence of a well-established experimental model for PMS, in contrast to the model of experimental autoimmune encephalomyelitis (EAE) for RRMS, might provide one explanation for this.
2 PMS is less common than RRMS, making clinical trial recruitment a more challenging task.
3 Although clinical relapse and new T2 lesion count are easy-to-measure outcome parameters in RRMS, definition and objective measurement of clinical and radiological progression are difficult tasks in PMS. Therefore, clinical trials in PMS need larger patient numbers and/or longer observation periods than RRMS trials to achieve significant results.
4 The time of onset of a patient’s first clinical relapse is easy to define in RRMS, while, in PMS, the onset is less clear and often definable only retrospectively. As a result, early initiation of a particular therapy, which is a prerequisite for a favourable treatment response in RRMS, is hard to achieve in PMS.

In response to the challenges, more than 50 phase II or III clinical trials including patients with PMS have been completed in the last 30 years.1 The majority of treatment regimes studied during this period includes immunosuppressants, chemotherapeutics or immunomodulators. Despite the large number of clinical trials, only three disease-modifying drugs have been approved for use in PMS by the US Food and Drug Administration (FDA) [mitoxantrone for secondary PMS (SPMS) and ocrelizumab (Ocrevus®, Roche) for primary PMS (PPMS)] or the European Medicines Agency (EMA) [mitoxantrone and interferon (IFN)β-1b (Betaseron®, Betaferon®, Schering) for SPMS; approval for ocrelizumab in PPMS is expected in late 2017].

Interferon β-1b

Interferon β-1b has been tested in two clinical trials in SPMS. The European SPMS (EUSPMS) trial1 recruited 718 patients in a randomized double-blind placebo-controlled phase III trial. Treatment with IFN-β1b resulted in a 22% reduction in the number of patients with 3 months of confirmed disability progression.
that was independent of baseline Expanded Disability Status Scale (EDSS) score, pre-entry relapse rate and the occurrence of relapses during the study. There was a significant reduction in clinical and magnetic resonance imaging (MRI) activity, which was of the same magnitude observed in the pivotal clinical trial in RRMS. In contrast, a subsequent study performed in North America failed to confirm the effect of IFN-β1b on disability progression, even if the efficacy of clinical and MRI measures of disease activity was confirmed. A comparison of the two studies revealed a younger and more active population in the EUSPMS trial, characteristics that are in line with a better response to anti-inflammatory treatments in patients with more active disease. Moreover, it is probable that a higher relapse rate during the study may have driven the EDSS changes, as the annualized relapse rate of 0.64 observed in the placebo arm of the EUSPMS trial is a value not observed even in pure RRMS clinical trials today.* A Cochrane Database Systematic Review concluded that IFNs do not reduce the risk of sustained 6-month EDSS progression in SPMS patients; however, there is a significant decrease in the risk of 3-month confirmed disability progression, reflecting relapse-related disability changes. Based on these results, the clinical use of IFNs in SPMS patients is restricted to the use of IFN-β1b in those with persisting attacks, and mostly to those with low levels of disability. The rationale for this is twofold: (1) these patients have some level of ongoing inflammatory activity that may respond to the drug and (2) IFNs increase spasticity, and the potential advantages of protection from new lesions are countered by adverse effects on the motor system.5

Mitoxantrone

Mitoxantrone is an antineoplastic anthracenedione derivative that inhibits DNA replication, DNA-dependent ribonucleic acid (RNA) synthesis and DNA repair, resulting in a marked reduction of B- and T-cell numbers. Mitoxantrone is a very small molecule and, therefore, is able to cross the blood–brain barrier (BBB) and interact with cells in the central nervous system (CNS).7,8 In the Mitoxantrone in MS (MIMS) trial,9 194 patients with worsening RRMS or SPMS (around half of the participants) were assigned placebo or mitoxantrone at a dose of 12mg/m² intravenously every 3 months for 24 months. At 24 months, mitoxantrone showed a significant benefit compared with the placebo group for disability progression confirmed at 3 and 6 months. However, the overall proportion of patients who progressed was low (19% in the placebo arm vs. 7% in the mitoxantrone arm) and a separate statistical analysis of the SPMS patients was not performed. Secondary outcome parameters (relapse rate and MRI parameters) also favoured mitoxantrone over placebo. However, the population included in the MIMS trial does not allow conclusions to be drawn on the efficacy of mitoxantrone in SPMS patients without attacks. Interestingly, an open-label study comparing the efficacy of mitoxantrone in RRMS and SPMS showed that the proportion of patients who experienced no disability progression was significantly higher in the RRMS group than in the SPMS group, in line with observations using IFNβ. The most important limitations of mitoxantrone are long-term safety concerns, specifically the risk of cardiotoxicity and acute leukaemia.11

Ocrelizumab

Ocrelizumab is a recombinant humanized antibody designed to selectively target cells that express the B-lymphocyte antigen CD20 on their surface. The CD20 molecule is an activated-glycosylated phosphoprotein expressed on a broad range of cells of the human B-cell lineage, with increasing concentrations from pre-B-cells through to naive and memory B-cells, whereas CD20 is not expressed on stem cells, pro-B-cells or differentiated plasma cells.12

Although T-cells and their role in the pathogenesis of MS have been extensively studied for decades, B-cells have attracted the attention of the MS medical community only recently. Two features that might be responsible for their pathogenic role in MS are (1) B-cells can produce proinflammatory cytokines and are potent antigen-presenting cells involved in the activation of proinflammatory T cells and (2) B-cells may differentiate into plasma cells that can produce autoantibodies directed against myelin and cause a complement-mediated attack on the myelin sheath.13 Studies of the pathology of MS have shown that ectopic lymphoid follicles resembling germinal centres containing B-cells and plasma cells are present in the meninges of patients with SPMS, indicating that B-cells migrate to the brain. Although reportedly restricted to late disease phases, the establishment of lymphoid-like structures in the brains of patients with MS suggests a pathophysiological role of B-cells in MS.14

Ocrelizumab was tested in a randomized double-blind placebo-controlled phase III trial – Ocrelizumab Versus Placebo in Primary Progressive Multiple Sclerosis

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in which 732 patients with PPMS received intravenous ocrelizumab (600mg) or placebo in a 2:1 ratio every 24 weeks for ≥120 weeks. The study met the primary end point with a significant reduction in 12-week confirmed disability progression. Secondary outcome parameters (24-week confirmed disability progression, performance on the 25-foot walk test and total brain volume loss) were also met. However, some discussion remains as to whether or not the study population truly reflects the whole population of PPMS patients. In particular, the clinical activity, with a median EDSS score of 4.5 after a median disease duration of 6 years, as well as the radiological activity, with 28% of patients with gadolinium-enhancing lesions, were quite high for a PPMS population. This is of particular interest because another PPMS phase III trial\textsuperscript{16} with a monoclonal CD20 antibody (rituximab) failed to show superiority when compared with placebo. In this study, the overall population showed less clinical and radiological activity. Moreover, a preplanned subgroup analysis suggested a significant effect in younger patients with gadolinium-enhancing lesions on brain MRI in terms of clinical and radiological activity.

In the ORATORIO trial,\textsuperscript{15} overall tolerability and safety were good, with infusion-related reactions, upper respiratory tract infections and oral herpes infections being the side-effects occurring more frequently with ocrelizumab than with placebo. Neoplasms occurred in 2.3% of patients who received ocrelizumab and in 0.8% of patients who received placebo. Although the incidence of neoplasms was extraordinarily low in the placebo group and within the normal range in the ocrelizumab group, some vigilance is mandatory in this respect. There was no clinically significant difference between groups in the rates of serious adverse events and serious infections.\textsuperscript{19} Sporadic cases of progressive multifocal leucoencephalopathy with rituximab, and one additional case in a patient with ocrelizumab in the post-marketing phase, are also worth noting.\textsuperscript{17}

Ocrelizumab was approved by the FDA for patients with PPMS in March 2017 and approval by the EMA is expected in late 2017. The therapy is applied as an infusion (2×300mg separated by 2 weeks) twice a year.

**Siponimod**

Siponimod (BAF312) is an oral modulator of sphingosine-1-phosphate receptor 1 (S1P1) that selectively acts on S1P1 and sphingosine-1-phosphate receptor 5 (S1P5), leading to a putative greater selectivity than the S1P1-5 agonist fingolimod (Gilenya®, Novartis).\textsuperscript{18} Siponimod inhibits egress of potentially autoaggressive lymphocytes into the circulatory system and consequently their infiltration of the CNS. Moreover, it may have direct CNS effects by modulating neurobiological processes via S1P1 and S1P5 on astrocytes and oligodendrocytes and has therefore been suggested to exert neuroprotective and regenerative actions in the CNS.\textsuperscript{19} A randomized double-blind placebo-controlled phase III trial of siponimod in patients with SPMS has recently been completed [Exploring the Efficacy and Safety of Siponimod in Patients With Secondary Progressive Multiple Sclerosis (EXPAND)]. Although not yet published, it has been revealed that siponimod reduced the risk of confirmed disability progression (the primary outcome) and met several other outcome parameters, but no change was observed in the 25-foot walk test.\textsuperscript{20}

**Adrenocorticotropic hormone**

Adrenocorticotropic hormone (ACTH) has been used for decades in the treatment of MS relapses owing to its steroidogenic properties. Recent data suggest that it also has additional corticosteroid-independent mechanisms. For instance, it has been suggested that ACTH exerts anti-inflammatory effects [via modulation of regulatory T-cells, inhibition of activation of nuclear factor kappa B (NF-κB) and possibly the triggering of CNS-restricted release of noradrenaline and acetylcholine] and may have neuroprotective effects in spinal cord injury and ischaemic brain injury.\textsuperscript{21,22} These aspects provided the rationale for an ongoing phase II trial (NCT01950234)\textsuperscript{23} of ACTH in PMS.

**Antiepileptic drugs**

It has been shown in experimental animal models that loading of partially demyelinated axons with sodium ions results in an accumulation of calcium ions, which triggers a cascade of degradative enzyme activity and finally leads to axonal degeneration.\textsuperscript{24} Consequently, partial blockade of sodium channels might have neuroprotective effects.\textsuperscript{25} As such, sodium-blocking agents such as phenytoin, lamotrigine and carbamazepine have been suggested as potential therapeutic strategies in PMS. Proof of this concept is still pending, because lamotrigine failed to show beneficial effects in a phase II trial\textsuperscript{26} versus placebo in
patients with SPMS. In contrast, lamotrigine treatment was unexpectedly found to be associated with greater annual cerebral volume loss in the first year than placebo. This effect was partially reversed after discontinuation of treatment. However, the rate of decline on the timed 25-foot walk test was significantly reduced in the treatment group. Interpretation of the results has been further complicated by a non-adherence rate of up to 50% in the lamotrigine group.

It is known that the use of steroids in the treatment of acute optic neuritis, a common manifestation of MS, has little or no impact on the eventual extent of recovery. Optical coherence tomography of the retinal nerve fibre layer and MRI of the optic nerve following optic neuritis have shown volume loss (neuroaxonal loss) in correlation with impaired visual function. In a phase II trial of phenytoin versus placebo in patients with acute optic neuritis, treatment with phenytoin within 2 weeks of symptom onset was accompanied by a 30% protective effect on retinal nerve fibre layer thickness and macular volume after 6 months of acute optic neuritis. A phase II trial (NCT02104661) of oxcarbazepine (Trileptal®, Novartis) in SPMS assessing the change in the content of neurofilament light chain in cerebrospinal fluid, a proposed surrogate marker of neurodegeneration, as well as clinical disability and imaging outcomes, is under way.

**Amiloride, fluoxetine and riluzole**

Amiloride is a potassium-sparing diuretic capable of inhibiting acid-sensing ion channels, a property that has been linked to possible neuroprotective effects. It has been found to reduce functional neurological deficits in EAE studies. However, a clinical trial of amiloride in patients with optic neuritis showed no positive effect in terms of optical coherence tomography parameters and was prematurely stopped. Riluzole is an inhibitor of tetrodotoxin-sensitive voltage-gated sodium channels, has an antiglutamatergic profile and is the only established disease-modifying treatment for amyotrophic lateral sclerosis. Fluoxetine is a selective serotonin reuptake inhibitor that has been suggested to have neuroprotective properties by suppression of microglial activation, NF-κB (a family of transcription factors with an essential role in inflammation and innate immunity) activity and enhancement of the production of the brain-derived neurotrophic factor in animal models. A four-arm phase II trial – Multiple Sclerosis-Secondary Progressive Multi-Arm Randomisation Trial (MS SMART) (NCT01910259) of amiloride, fluoxetine and riluzole compared with placebo in patients with SPMS is currently under way, using novel outcome parameters including neurofilament and modern MRI techniques.

**Anti-leucine-rich repeat and immunoglobulin-like domain-containing protein 1**

Leucine-rich repeat and immunoglobulin-like domain-containing protein 1 (LINGO-1) is a cell surface protein expressed in neural cells, and a negative modulator of axonal myelination via inhibition of the differentiation of oligodendrocyte precursor cells to mature oligodendrocytes. Blockage of LINGO-1 may therefore represent a potential strategy for remyelination and axonal preservation in MS. In an EAE study, anti-LINGO-1 antibodies improved axonal integrity and new myelin sheath formation, resulting in functional recovery.

In a recent randomized double-blind placebo-controlled phase II study – Safety and Efficacy of Opicinumab in Acute Optic Neuritis (RENEW) – participants with a first unilateral acute optic neuritis episode within 28 days of study baseline were assigned to receive either 100mg/kg opicinumab intravenously or placebo once every 4 weeks (six doses) in addition to a standardized regimen of high-dose methylprednisolone. The primary end point was remyelination at 24 weeks, measured as the recovery of affected optic nerve conduction latency using full-field visual evoked potential (VEP) versus the unaffected fellow eye at baseline. Analysis was by intention to treat (ITT) and prespecified per protocol (PP) analyses were also conducted. Remyelination did not differ significantly between the opicinumab and placebo groups in the ITT population at week 24. However, results from the prespecified PP population suggest that enhancing remyelination in the human CNS with opicinumab might be possible and warrants further clinical investigation. In a post hoc analysis, a subgroup of patients identified by novel MRI techniques (diffusion tensor imaging and magnetization transfer imaging) had a more favourable outcome. These techniques are used as additional inclusion criteria in an ongoing
trial – Efficacy and Safety of BIIB033 (Opicinumab) as an Add-On Therapy to Disease-Modifying Therapies (DMTs) in Relapsing Multiple Sclerosis (MS) (AFFINITY) (NCT03222973) – with opicinumab versus placebo as an add-on therapy to a standard immunomodulatory treatment in patients with RRMS.

**Biotin**

Biotin is a water-soluble vitamin belonging to the B complex family and an essential micronutrient that acts as a cofactor for decarboxylase enzymes. High doses of biotin have been found to prevent the course of biotin-responsive basal ganglia disease, an autosomal recessive subacute encephalopathy in childhood. In a case series of patients with relapsing episodes of ataxia and optic neuropathy, radiological findings suggested that leucodystrophies also responded to high doses of biotin. One of those patients was later diagnosed with SPMS. This was the rationale for an open-label pilot study of high-dose biotin (100–300 mg/day) in patients with SPMS and PPMS, which showed a positive impact on disease progression in patients with optic nerve and spinal cord involvement. A subsequent phase III trial of high-dose biotin (MD1003) in PMS showed an improvement in the EDSS in 13% of the treatment group compared with 0% in the placebo group. Similar improvement was achieved in the timed 25-foot walk test. Although the primary outcome parameter was achieved with statistical significance, some discussion remains about the magnitude of the observed effect (e.g. 0.2 points in the EDSS). Further trials are necessary to clarify whether or not high-dose biotin is a clinically meaningful option in PMS therapy.

**Domperidone**

Dopamine is a key player in the regulation of prolactin secretion, achieved mainly by inhibiting the anterior pituitary lactotrophs. Domperidone is a dopamine-2 receptor antagonist widely used in Canada and Europe as a prokinetic agent for gastroparesis, with the induction of lactation (via increasing prolactin secretion) as one possible side-effect. EAE studies suggest that prolactin can promote myelin repair and thereby may have a potential role as a remyelinating therapy in MS. This is in line with the observation of the beneficial effect of pregnancy in reducing disease activity in MS, an observation that may be, in part, related to higher prolactin levels. Consequently, a phase II trial (NCT02308137) of oral domperidone in patients with SPMS is currently in progress.

**Erythropoietin**

In animal models of several neurological diseases, erythropoietin (EPO) has been shown to have antioxidative, anti-inflammatory and neurotrophic effects. Accordingly, EPO has been shown to reduce clinical severity, axonal injury and demyelination, and diminish glial expression of major histocompatibility complex class II in the EAE model. A small open-label pilot study of EPO in patients with PMS showed both clinical and electrophysiological improvement of motor function with high-dose EPO. Similarly, EPO showed beneficial results on retinal nerve fibre layer thinning, a decrease in retrobulbar diameter of the optic nerve and VEP latencies in patients after optic neuritis in a phase II placebo-controlled trial. A phase II trial (NCT01144117) of EPO in PMS has recently been completed but results have not yet been released.

**Haematopoietic stem cell therapy**

Haematopoietic stem cell transplantation has been proposed as a second-line therapy for refractory MS. Although early clinical trials in PMS revealed only moderate efficacy on short-term clinical outcomes, long-term follow-up results of a single-centre trial suggested a more robust improvement in the disease progression-free survival rate, at least in those patients with active inflammation. In addition, several efforts to improve technical issues (optimization of the cell source and patient selection) and the safety and tolerability of the procedure have been made in recent years. In particular, the use of mesenchymal stem cells or autologous unfractionated bone marrow cells, without the need for preceding immunosuppression, has improved the tolerability of the procedure. This strategy was used in an open-label proof-of-concept trial in patients with SPMS with clinical evidence of optic nerve involvement. The study showed improved visual acuity and visual evoked response latency, and an increase in the optic nerve diameter, after infusion of autologous bone marrow-derived mesenchymal stem cells. A phase II trial (NCT01815632) of autologous bone marrow infusion in patients with SPMS or PPMS (ACTiMuS) is currently recruiting participants.
Ibudilast

Ibudilast is a non-selective phosphodiesterase inhibitor that has been suggested to have immunomodulatory and neuroprotective effects by inhibiting leukotrienes and nitric oxide synthesis, and reducing tumour necrosis factor-α from astrocytes and microglial cells. A phase II trial of ibudilast in patients with RRMS failed to show a positive effect on the number of new gadolinium-enhancing MRI lesions but showed some beneficial effect on brain atrophy, suggesting a potential neuroprotective mechanism of the compound. A phase II brain atrophy trial (NCT01982942) of ibudilast in PMS was completed in May 2017 and results are expected soon.

Idebenone

Idebenone is a synthetic analogue of coenzyme Q10, an endogenous antioxidant found in all cellular membranes and a constituent of the ATP-producing electron transport chain of mitochondria. In addition to antioxidant properties, idebenone has been shown to exert anti-inflammatory effects in vitro. Idebenone use in Friedreich’s ataxia and Leber’s hereditary optic neuropathy, both of which are thought to be mitochondrial disorders, has shown beneficial effects. In a recent animal study, idebenone was found to protect hippocampal HT22 cells from glutamate-induced cell death in vitro, although idebenone-treated EAE mice did not exhibit any clinical benefit with respect to reducing inflammation, demyelination and axonal injury. Given that mitochondrial dysfunction may play a key role in progressive axonal loss in MS, further investigations into a therapeutic option for PMS are rational. A phase II trial (NCT01854359) of idebenone in PPMS is currently under way.

Lipoic acid

Lipoic acid is a natural antioxidant with signal transduction modulatory pathways, and has been suggested as a potential therapeutic agent in diseases associated with oxidative stress such as diabetic neuropathy, Alzheimer’s disease and MS. Lipoic acid has been shown to suppress EAE by inhibiting the entry of T-cells into the CNS. In a recent small phase I study, lipoic acid was well tolerated in patients with MS and was associated with a reduction in matrix metalloproteinase-9 and soluble intercellular adhesion molecule-1. A phase II/III trial (NCT01888811) of lipoic acid in patients with SPMS has been completed and results are pending.

Lithium

Lithium is one of the oldest antipsychotic drugs. Its therapeutic effects are mediated through inhibition of glycogen synthase kinase-3, a serine/threonine-protein kinase and major regulator of inflammation. Pretreatment with lithium has been shown to suppress disease activity onset in EAE in animals. Even when lithium was administered after the induction of EAE, it was able to reduce disease severity and facilitate symptom recovery. A pilot phase I/II trial (NCT01259388) of lithium in PMS has been completed and results are pending.

Masitinib

Masitinib is a selective tyrosine kinase inhibitor that modulates migration, survival and degranulation of mast cells. It has been restricted to use only in veterinary medicine and human mast cell tumours. Increasing evidence suggests that mast cells also play a role in pathogenesis of MS by releasing vasoactive mediators that sustain inflammatory cascade, disrupting the BBB and stimulating activated T-cells, among other mechanisms. In a phase IIa proof-of-concept trial, masitinib was well tolerated and found to have a positive but not statistically significant effect on clinical progression in patients with PMS. A phase Ib/II (NCT01433497) study of masitinib in patients with relapse-free SPMS or PPMS is in progress.

MIS416

MIS416 is a myeloid-directed microparticle immune response modifier (derived from Propionibacterium acnes), which was originally developed as a vaccine adjuvant. MIS416 has been suggested to modulate T-cell-mediated autoimmune responses in EAE by simultaneously activating innate toll-like receptor 9 and nucleotide-binding oligomerization domain-containing protein 2. The restricted uptake of MIS416 by phagocytic cells has been suggested to lead to targeted modulation of the innate immune system. MIS416 was initially used in patients with SPMS outside a formal clinical trial setting under compassionate use legislation in New Zealand. In a phase Ib/IIa clinical trial, MIS416 was shown to suppress the development of proinflammatory
T-helper 1, 2 and 17 cells in EAE and to increase the serum levels of IFN-γ and IFN-γ-associated proteins in 19 patients with SPMS. A phase IIb trial showed good safety and tolerability of the compound, suggesting that further trials would be valuable to determine clinical efficacy.

Simvastatin

Statins (hydroxymethylglutaryl-CoA reductase inhibitors) are widely prescribed and well tolerated in the treatment of hypercholesterolaemia. However, they also exert immunomodulatory and neuroprotective properties and have been shown to improve cerebrovascular haemodynamics. These properties make statins an attractive candidate drug in patients in the later stages of MS when dysfunction of brain parenchymal cells and vascular endothelial cells occurs. Studies of statins in EAE and open-label trials in patients with MS have shown decreased disease activity. In a phase II trial of simvastatin versus placebo in patients with SPMS, simvastatin was found to significantly reduce the annualized rate of whole-brain atrophy compared with placebo by 43%. These results provide support for the advancement to a phase III trial of statins for PMS.

Sunphenon epigallocatechin-3-gallate

Sunphenon® (Taiyo International) epigallocatechin-3-gallate (EGCg), a major constituent of green tea, has been suggested as a neuroprotective compound in several neurological disorders by mediating reactive oxygen species. In EAE studies, EGCg has been shown to have anti-inflammatory properties by influencing T-cell proliferation and inhibiting the activation of NF-kB, and neuroprotective properties by acting as a free radical scavenger. A phase II/III trial of simvastatin versus placebo in patients with SPMS was found to significantly reduce the annualized rate of whole-brain atrophy compared with placebo by 43%. These results provide support for the advancement to a phase III trial of statins for PMS.

Conclusion

The long list of therapeutic agents currently in development for the treatment of PMS, and the fact that the first agents for PMS showed significant efficacy in randomized placebo-controlled clinical trials, provides some reason for optimism in the therapeutic fields of PMS. Moreover, increased knowledge about the pathophysiological basis of PMS and the development of improved clinical trial design will further increase the chance that new therapeutic targets will eventually be identified and successfully pass clinical trial programmes in patients with PMS.

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Extending the opening hours of family medicine clinics will reduce load on emergency departments – effects on the early detection of limb fractures

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Abstract

Patients with serious and non-serious limb complaints are diverted to emergency departments (EDs) at night, when regular clinics are closed. This study was conducted to identify the impact of extending the opening hours of family medicine (FM) clinics on the detection of limb fractures in patients with limb complaints, which could be a measure of expected patient influx in EDs. A cross-sectional comparative study was conducted in a health centre in Dubai, United Arab Emirates. Patients with limb complaints were categorized by attendance during regular hours (7:30–21:30 hours) and extended hours (21:30–7:30 hours). Rates of fracture positivity, patients handled by the FM clinic and patients referred by the FM clinic to other departments were analysed. SPSS Statistics version 24 (IBM Corporation, Armonk, NY, USA) was used for analysis; chi-squared tests were used to determine association and P-values <0.05 were considered significant. A total of 736 patients with limb complaints were studied: 81.79% (602) attended the FM clinic during regular hours and 18.21% (134) attended during extended hours. The total number of fracture-positive patients was 108. Fracture positivity was more frequent during extended hours: 23 of 134 (17.16%) patients were fracture positive during extended hours and 85 of 602 (14.11%) patients were fracture positive during regular hours. Only 30 of 134 (22.38%) patients were referred to the ED or another department during extended hours, whereas 150 of 602 (24.91%) patients were referred to the ED or another department during regular hours. Referral of fracture-positive patients was not affected by time of attendance (P>0.05). More fracture-positive patients and fewer referrals during extended hours indicates the significance of extending clinic opening hours; extending the opening hours of this clinic to 24 hours indirectly reduced ED crowding.

Introduction

Family physicians, often known as primary care physicians, are qualified to provide essential health care for all ages and for most ailments.1 The usual opening hours of any functioning clinic within a hospital are during the day. Once these clinics are closed, patients with both serious and non-serious complaints are diverted to emergency departments (EDs), which can lead to ED crowding: one study has reported that as many as 55.4% of all cases in EDs are non-urgent.2 This situation has been regularly reported for EDs in the United States, which frequently function at or over 100% capacity.3 Musculoskeletal injuries account for about 50% of presentations to ED;4 among which trauma-related fractures, which can lead to morbidity, mortality and compromised quality of life, including increased medical costs and lasting disabilities, are relatively common.4,5 In recent studies, the annual incidence of hospitalization as a result of injury has ranged from 65 to 136 per 100000.6,7 The incidence of trauma-related death in the United Arab Emirates (UAE) is 7.4 per 100000.8 Hence, it is very important that patients are diagnosed both promptly and efficiently. At night, when clinics are closed, patients with limb complaints, including patients with limb trauma, present at EDs for acute management. The consequences for these patients include unreasonably extended waiting times due to their comparatively low priority.

The UAE is a fast-developing country with a population of more than 6 million. Until recently, in the south of Dubai a 24-hour government
emergency facility was provided only by hospitals more than 30 km from Al-Barsha Health Center. Al-Barsha Health Center plays an important role in medical care for the local community and expatriates, serving a population of over 60000 residing in and around the Al-Barsha area. As a result of its location and the high demand for its medical services, Al-Barsha Health Center was converted from a regular clinic to a 24-hour clinic in September 2013. This was necessary to reduce the burden of patients presenting to the ED (where family physicians were available 24 hours to deal with emergency and non-emergency cases), which had led to an increased mortality rate among hospital inpatients. Furthermore, an overcrowded ED makes it more likely that patients will leave against medical advice or without being seen at all (13–20%).\textsuperscript{10,11} The situation is at its worst at night, when the proportion of patients leaving the ED because of crowding and without being seen at all is double that during the day.\textsuperscript{10} Hence, it seems that a night-time clinical service, which could be available as an ambulatory service, would be an effective way to reduce ED crowding. Therefore, it can be speculated that extending family medicine (FM) clinics’ opening hours to 24 hours will both indirectly reduce the burden on EDs and increase patient satisfaction.

Understanding the benefits of extending the opening hours of a health centre is necessary in order to present evidence-based recommendations for the improvement of treatment facilities and future medical services. We sought to identify the impact of increasing FM clinic opening hours from regular to extended hours on the detection of limb fractures. To achieve this aim, we compared the frequency of limb complaints and fractures during regular hours and extended hours. The relationship between fracture positivity, number of patients handled by the FM clinic and number patients referred by the FM clinic to another department was also investigated. Additionally, the site of injury (upper or lower limb) and its association with fracture positivity and patient referral were compared for both regular and extended hours.

**Materials and methods**

A cross-sectional comparative study was carried out at Al-Barsha Health Center in Dubai, UAE. The opening hours of the clinic were categorized as regular hours (7:30–21:30 hours) and extended hours (21:30–7:30 hours). Data were compiled over a 3-month period from the date of ethics review committee approval (DSREC-07/2015_04): 1 January 2015 to 31 March 2015. Data were included for patients who underwent limb radiography at Al-Barsha Health Center during that period.

All registered Al-Barsha Health Center patients undergoing limb radiography during the period of study were included; patients undergoing limb radiography outside Al-Barsha Health Center were excluded. A list of all limb radiography that was carried out at Al-Barsha Health Center during the period of study was compiled by the investigator from medical records. All data were confidential and no personal information was shared with unauthorized parties.

Data on the influx of patients and diagnoses of fractures during the same 3 months (1 January 2015 to 31 March) of 2013, when regular clinics were operational but extended opening hours had not been introduced, were collected by the same means and compared with the 2015 data.

Demographic data for all study participants were documented, including age, sex and nationality.

The total number of patients was recorded, and patients were categorized by time of attendance: during regular hours or extended hours. Fracture positivity in all patients – patients who attended during regular hours and patients who attended during extended hours – was documented. The number of patients handled by the FM clinic and the number of patients referred by the FM clinic to the ED or another department was documented for all patients. Site of injury, sick leave and time of radiography were also documented for all patients.

Fractures were diagnosed by radiography. Descriptive statistics, frequencies and proportions were calculated for categorical variables such as sex, site of fracture, referral and sick leave. Mean and standard deviations were calculated for age. SPSS Statistics version 24 (IBM Corporation, Armonk, NY, USA) was used for analysis; chi-squared tests were used to determine association and \( P \)-values <0.05 were considered significant.
Results

A total of 736 patients were studied between 1 January 2015 and 31 March 2015. A total of 59.1% (435) were male and 40.9% (301) were female, with a mean age of 27.77±18.34 years, indicating no significant difference between the total number of male and female patients. A total of 86.1% (634) were nationals and 13.9% (102) were non-nationals. The mean age of patients who attended during regular and extended hours was 29.26±19.05 years and 23.41±15.09 years, respectively.

Of all 736 patients who attended the FM clinic, 81.79% (602) attended during regular hours and 18.21% (134) attended during extended hours. Comparing the number of male and female patients who attended during regular and extended hours, the majority of patients who attended during extended hours were male (71.7%, 96 of 134; \( P < 0.001 \)). However, there was no significant difference during regular hours, when 56.3% (339 of 602) were male and 43.7% (263 of 602) were female.

When the presence of fracture was assessed, we found that 14.7% (108) of the total of 736 patients were fracture positive and 85.3% (628) were fracture negative, as shown in Table 1.

Of the patients who attended during regular hours (602), 14.11% (85) were fracture positive. Of the patients who attended during extended hours (134), 17.16% (23) were fracture positive. Though more patients were fracture positive during extended hours, this difference was not statistically significant.

The frequency of fracture positivity in male and female patients was determined. Of the 435 male patients across both regular and extended hours, 17.5% (76) were fracture positive. Of the 301 female patients across both regular and extended hours, 10.6% (32) were fracture positive. Overall, more males were diagnosed with fractures than females (\( P < 0.05 \)).

Of the total number of patients (736) who presented to the FM clinic, 75.6% (556) were handled by the FM clinic and 24.4% (180) were referred to the ED or another department: 95 (12.9%) patients were referred to the ED and 85 (11.5%) patients were referred to another department. Significantly more patients were handled by the FM clinic than were referred to the ED or another department (\( P < 0.05 \)).

Of the 602 patients who attended during regular hours, 24.91% (150) were referred to the ED or another department and 75.1% (452) were not. In comparison, of the 134 patients who attended during extended hours, 22.3% (30) were referred and 77.6% (104) were not. Referrals were made when patients – fracture positive or fracture negative – required intervention that was beyond the scope of the FM clinic. Though more patients were referred to the ED or another department during regular hours, this difference was not statistically significant (\( P > 0.05 \)).

There were significantly more referrals to the ED than to other departments (\( P < 0.05 \)).

The data for referrals were further evaluated against fracture positivity: 60.2% (65 of 108) of fracture-positive patients were referred and 39.8% (43 of 108) of fracture-positive patients were not. Referral by the FM clinic for fracture-positive patients was not affected by time of attendance (regular or extended hours) (\( P > 0.05 \)). There was also no effect (\( P > 0.05 \)) of the site of injury on referral.

TABLE 1 Management of patients with limb complaints during regular vs. extended hours

<table>
<thead>
<tr>
<th></th>
<th>Regular hours, ( n ) (%)</th>
<th>Extended hours, ( n ) (%)</th>
<th>Total number</th>
</tr>
</thead>
<tbody>
<tr>
<td>Number of patients undergoing radiography</td>
<td>602 (81.79)</td>
<td>134 (18.21)</td>
<td>736</td>
</tr>
<tr>
<td>Male</td>
<td>339/602 (56.30)</td>
<td>96/134 (71.70)</td>
<td>435</td>
</tr>
<tr>
<td>Female</td>
<td>263/602 (43.70)</td>
<td>38/134 (28.30)</td>
<td>301</td>
</tr>
<tr>
<td>Patients handled by the FM clinic</td>
<td>452/602 (75.10)</td>
<td>104/134 (77.60)</td>
<td>556</td>
</tr>
<tr>
<td>Patients referred to the ED or another department</td>
<td>150/602 (24.91)</td>
<td>30/134 (22.30)</td>
<td>180</td>
</tr>
<tr>
<td>Fracture-positive patients</td>
<td>85/602 (14.11)</td>
<td>23/134 (17.16)</td>
<td>108</td>
</tr>
<tr>
<td>Handled by the FM clinic</td>
<td>34/85 (40.00)</td>
<td>9/23 (39.13)</td>
<td>43</td>
</tr>
<tr>
<td>Referred to the ED or another department</td>
<td>51/85 (60.00)</td>
<td>14/23 (60.86)</td>
<td>65</td>
</tr>
</tbody>
</table>
Additionally, history of trauma was assessed: 66.98% (493 of 736) of patients had a history of trauma ($P<0.05$), 25.13% (185 of 736) of patients did not; trauma history was not documented for 7.88% (58 of 736) of patients.

Patients presenting with a history of trauma had a higher chance of fracture positivity than patients with no history of trauma (96.29%, $P<0.01$), as elaborated in Table 2. The chance of fracture positivity was higher for patients with a history of trauma in both regular hours ($P<0.05$) and extended hours ($P<0.05$).

Assessment of the number of patients on sick leave showed that only 21.2% (156 of 736) of patients were on sick leave. The distribution of fracture positivity and sick leave is shown in Table 3.

There was no association between fracture positivity and sick leave ($P>0.05$), nor between patient sex and sick leave ($P>0.0$), among either fracture-positive or -negative patients. The taking of sick leave was also not affected by time of attendance (regular or extended hours). Of the fracture-positive patients who attended during regular hours (85 of 108), 22.35% were on sick leave and 77.65% were not. Similar results were found for patients who attended during extended hours: of the fracture-positive patients who attended during extended hours (23 of 108), 21.74% (5 of 23) were on sick leave and 78.26% (18 of 23) were not. The number of fracture-positive patients who attended during extended hours was not affected by sick leave ($P>0.05$).

### TABLE 2 History of trauma and fracture positivity

<table>
<thead>
<tr>
<th>Fracture</th>
<th>History of trauma</th>
<th></th>
<th></th>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Yes, $n$ (%)</td>
<td>No, $n$ (%)</td>
<td>Unknown, $n$ (%)</td>
<td>Total</td>
<td></td>
</tr>
<tr>
<td>Positive</td>
<td>104 (96.29)</td>
<td>3 (2.7)</td>
<td>1 (0.92)</td>
<td>108</td>
<td></td>
</tr>
<tr>
<td>Negative</td>
<td>389 (61.9)</td>
<td>182 (28.98)</td>
<td>57 (9.07)</td>
<td>628</td>
<td></td>
</tr>
<tr>
<td>Total</td>
<td>493 (66.98)</td>
<td>185 (25.13)</td>
<td>58 (7.88)</td>
<td>736</td>
<td></td>
</tr>
</tbody>
</table>

### TABLE 3 Fractures and sick leave

<table>
<thead>
<tr>
<th>Fracture</th>
<th>Sick leave</th>
<th></th>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Yes, $n$ (%)</td>
<td>No, $n$ (%)</td>
<td>Total</td>
<td></td>
</tr>
<tr>
<td>Positive</td>
<td>18 (16.66)</td>
<td>90 (83.33)</td>
<td>108</td>
<td></td>
</tr>
<tr>
<td>Negative</td>
<td>138 (21.97)</td>
<td>490 (78.02)</td>
<td>628</td>
<td></td>
</tr>
</tbody>
</table>

The mean number of days taken to provide a radiography report was $1.32\pm0.273$ overall: $1.28\pm1.87$ days for patients who attended during regular hours and $1.32\pm2.28$ days for patients who attended during extended hours. The number of days taken to provide a radiography report was not affected by time of attendance.

The number of days taken to provide a radiography report was not affected by fracture positivity ($P>0.05$).

The majority of patients (67.4%) received their radiography report within 1 day. The number of days taken to provide a radiography report ranged from 1 to 17.

Upper limb complaints were more common than lower limb complaints [412 of 736 (55.97%) vs. 315 of 736 (42.79%)], respectively and some patients (1.22%, 9 of 736) had both upper and lower limb complaints.

More patients with upper limb complaints were fracture positive (52.8%, 57 of 108) than patients with lower limb complaints (47.2%, 51 of 108), though this difference was not statistically significant.

Of all fracture-positive patients (108), 57 had upper limb fractures. Of these, 21 patients were handled by the FM clinic, 31 patients were referred to ED and five patients were referred to another department.

The FM clinic’s opening hours in 2013 were 7:30–21:30 hours; however, radiography was unavailable from 14:00 hours. The details of patients with limb complaints who attended the FM clinic in 2013 are given in Table 4.

### Discussion

This study was conducted to identify the effect of increasing the opening hours of FM clinics from regular hours (7:30–21:30 hours) to extended hours (24 hours) on the early detection of limb fractures in patients with limb complaints. For this purpose, data for patients presenting during regular hours and extended hours at Al-Barsha Health Center over a 3-month period were analysed and compared.

An initial assessment of variables revealed that the number of patients who attended during extended hours was lower than the number of
patients who attended during regular hours, which is understandable: patients who present during extended hours are typically those who seek urgent help and cannot wait for the next-day opening of clinics. The greater influx of male patients during extended hours is also understandable: traumatic injuries at night are typically caused by accidents, and cultural factors limit the liberty of women to wander at night-time, reducing the potential for accidents. Additionally, more patients were fracture positive during extended hours than during regular hours (17.16% vs. 14.11%), which indicates the significance of extending clinic opening hours. There were more fractures in patients presenting with upper limb complaints than lower limb complaints, but the difference was not statistically significant. This is in contrast to previous reports that the most common site of trauma-related fractures is the lower limb (41%), followed by the upper limb (29%). However, the population and study design in those studies were notably different.

To understand the significance of extended opening hours, we next considered patients referred by the FM clinic to the ED or another department to understand FM clinic capacity to diagnose and manage limb complaints. A significant number of patients were handled in the FM clinic and significantly fewer patients were referred (75.6% vs. 24.4%; \( P < 0.05 \)). Of the referred patients, 12.9% were referred to the ED and 11.5% were referred to another department.

Since the aim of the study was to understand the capacity of FM clinics to manage limb complaints during extended clinic opening hours, we analysed the number of patients who were handled by the FM clinic and the number of referrals during extended hours. It was found that only 22.38% of the total patients attending the FM clinic during extended hours were referred and 77.62% were handled by the FM clinic. Thus, it can be deduced that at least 77.62% (104 of 134) of patients with limb complaints may have presented to the ED for acute management if the FM clinic had not been available, which could have led to ED crowding. Numerous studies report that ED crowding is associated with poor performance for major trauma patients, high rates of patients leaving the ED without being seen and poor patient outcomes. Furthermore, it has been shown to lead to greater mortality in both patients admitted to the hospital and discharged patients. In a population study in Canada, it was estimated that the number of deaths in EDs could be reduced in high-risk and low-risk patients by 6.5% and almost 13%, respectively, if the length of stay in the ED is decreased by merely 1 hour. Hence, extending FM clinic opening hours and handling a significant number of patients may have indirectly reduced ED crowding.

One advantage of managing patients with limb complaints at FM clinics during extended hours is reduced waiting times, ensuring more timely management. Patients with limb complaints often require acute care, and in EDs they are classified as low priority, in contrast to life-threatening cases. This is particularly significant for Al-Barsha Health Center since there are no government hospitals in a 30km vicinity: the load of patients seeking emergency care falls on Al-Barsha Health Center’s ED.

One area that requires further investigation is the accuracy of fracture diagnosis by FM physicians. Studies report that FM physicians on a rotation of an average of 5 weeks in an orthopaedic service during their training show significantly less confidence in the management of musculoskeletal conditions than those on a rotation of 8 weeks or more. Earlier, a hospital set-up that adopted a rapid review process, which involved an on-call orthopaedic consultant for overnight radiography in
an ED that cross-checked with reported diagnosis, proved to be very efficient in terms of both cost and patient satisfaction.\textsuperscript{17} Hence, another suggestion for improving an FM clinic’s qualitative outcomes is to recruit an on-call orthopaedic consultant/radiologist for some or all patients during the hours of closure of the clinic as a part of a rapid review process. This could significantly improve the diagnostic and management outcomes as well as play a role in training the FM clinic in diagnosing and managing limb complaints.

Another aspect of the study worth addressing is the high number of fracture-positive patients who were referred. Of the 134 patients who presented during extended hours, 23 were fracture positive. Of these, 60.8\% (14 of 23) were referred and only 39.2\% were handled by the FM clinic. This calls into question the benefit of FM clinics if more than 60\% of fracture patients are referred. However, it is worth mentioning here that the rate of referral of fracture-positive patients was similar during both regular and extended hours, which indicates that the quality of care during extended hours is not compromised and that some complicated fractures are simply beyond the scope of FM clinics. The FM clinic of Al-Barsha Health Center has the facility to provide basic care such as dressing, stabilizing fractures with slabs and pain management. However, like other ambulatory clinics, it is not equipped to deal with complicated procedures and therefore such fracture patients are referred to the ED. Hence, it can be confidently deduced that management capacity was not compromised during extended hours: patients with fractures who were referred to the ED required ED services. By managing the majority of patients with limb complaints during extended hours, the FM clinic ensured that only patients requiring ED services reached the ED. Additionally, fracture-positive patients who are referred by the FM clinic to the ED are likely to have had their level of emergency and radiography needs assessed, and may have received some form of pain management, in cases where the injury is not life threatening. This early management of patients with limb complaints can avoid unnecessary waiting times for primary diagnosis and management.

The data for extended hours over the 3-month period showed a total of 134 patients with limb complaints arriving at the FM clinic, which means that, on average, 1–2 patients presented each night with limb complaints. Owing to the smaller number of patients with limb complaints who were handled per night, the cost of running a clinic compared with the cost avoided by the ED is called into question. It is therefore important to note that the FM clinic was catering for other complaints – serious and non-serious – in addition to limb complaints during extended hours, which could justify the cost of these extended opening hours.

In order to generate quantitative data, we intend to expand this study to investigate the impact of 24-hour FM clinic opening hours on ED crowding, inpatient waiting times, number of patients leaving the ED without being seen and patient satisfaction. In addition, we also intend to investigate the frequency and nature of presentations to the FM clinic during extended hours.

This study is the first to investigate the effects of extended clinic opening hours on the diagnosis of limb complaints. Data on the influx of patients and diagnosis of fractures were compared with data from 2013 for the same 3-month period, since, during the 2013 period, the FM clinic was operational during regular hours only. However, there are limitations here, as the data from the two 3-month periods are not directly comparable: during 2013, radiography was available only until 14:00 hours. By extending opening times, the FM clinic’s capacity was increased, enabling the clinic to manage a greater number of patients in 2015 than in 2013 (602 patients during regular hours in 2015, compared with 78 in 2013).

Conclusion

We recommend that future studies seek to establish the correlation between extended FM clinic opening times and ED crowding by recording ED influx and outflow before and after the introduction of extended opening hours. In this study we report that extended FM clinic opening hours facilitates the effective management of patients with limb complaints and may reduce ED crowding.

References


CASE REPORT

Superior mesenteric artery syndrome – a rare diagnosis for common upper gastrointestinal symptoms

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Abstract
Superior mesenteric artery (SMA) syndrome is a rare acquired vascular compression disorder in which acute angulation of the SMA results in compression of the third part of the duodenum, leading to intestinal obstruction. This is typically caused by an angle of 6–25° between the abdominal aorta and the SMA, in comparison with the normal range of 38–56°, as a result of a lack of retroperitoneal visceral fat (mesenteric fat). In addition, the aortomesenteric distance is 2–8mm as opposed to the typical 10–20mm. Here we report the case of an 11-year-old girl who presented with frequent attacks of non-specific abdominal pain over a few years, who had been treated symptomatically without a clear diagnosis. However, in the last admission, she presented to our hospital with symptoms of subacute small bowel obstruction including bilious vomiting and epigastric pain that prompted extensive investigations including multislice abdominal computerized tomography with oral and intravenous contrast. This scan confirmed the diagnosis of SMA syndrome.

Introduction
Superior mesenteric artery (SMA) syndrome, first described by Von Rokitanski in 1861,1 is a rare acquired vascular compression disorder in which acute angulation of the SMA results in the compression of the third part of the duodenum, leading to obstruction.2 The syndrome is typically caused by an angle of 6–25° between the abdominal aorta and the SMA, in comparison with the normal range of 38–56°, as a result of a lack of retroperitoneal visceral fat (mesenteric fat). In addition, the aortomesenteric distance is 2–8mm as opposed to the typical 10–20mm. It is seen more frequently in females, and usually occurs in older children and adolescents.

Patients often present with chronic upper abdominal symptoms, such as epigastric pain, nausea, eructation, copious vomiting (bilious or partially digested food), postprandial discomfort, early satiety and sometimes subacute small bowel obstruction.4

Diagnosis is very difficult and usually by exclusion of other causes. Standard examinations include abdominal and pelvic computerized tomography (CT) with oral and intravenous contrast, upper gastrointestinal series and, in equivocal cases, hypotonic duodenography. In addition, vascular imaging studies, such as ultrasound and contrast angiography, may reveal increased blood flow velocity through the SMA or a narrowed SMA angle.5,6 Measuring the aortomesenteric distance and angle is the gold standard for the diagnosis of SMA syndrome.

Our patient presented with history of frequent attacks of non-specific abdominal pain over a few years that had been treated symptomatically without a clear diagnosis. However, in the last admission, she presented to our hospital with abdominal pain, vomiting and a frank clinical picture of subacute small bowel obstruction that prompted extensive investigation, including multislice abdominal CT with oral and intravenous contrast administration. This confirmed the diagnosis of SMA syndrome.

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Case report

A Bangladeshi girl aged 11 years presented to the emergency room (ER) with a 1-day history of diarrhoea, non-bilious vomiting and abdominal pain. The patient was thin, mildly dehydrated and in moderate pain. Abdominal examination revealed mild periumbilical and epigastric tenderness without distension or organomegaly.

She was admitted to the ER, given i.v. fluid and nil by mouth. A few hours later she was able to tolerate oral feeding without vomiting or abdominal pain, and was discharged home. However, the next day, she again presented with severe epigastric abdominal pain with nausea and non-bilious vomiting, but without diarrhoea, and was admitted to the paediatric ward for observation and to rule out appendicitis.

The patient had a history of three hospital admissions with similar attacks of abdominal pain and vomiting at the ages of 3, 7 and 10 years. All previous investigations were non-conclusive and the diagnosis was non-specific abdominal pain with acute gastritis.

Upon admission to the paediatric ward she vomited bile three times and exhibited mild dehydration (3%). The pain was predominantly epigastric with no signs of peritoneal irritation and no abdominal distension. C-reactive protein was negative and a complete blood count, liver enzymes and function, urea and electrolytes were all normal. The surgeon advised continued observation and abdominal radiography and ultrasonography; both were unrevealing and findings were normal.

The patient’s pain persisted for another 3 days accompanied by vomiting attacks despite the fact that she was receiving only i.v. fluid. As a result a paediatric gastroenterologist was consulted and recommended carrying out a upper gastrointestinal water-soluble oral contrast fluoroscopic follow-through study. However, this was not tolerated by the patient as she continued to vomit even after prescribing antiemetic drugs.

After team discussion, post-intravenous, oral contrast, multislice, abdominal CT revealed a reduced aortomesenteric artery distance, reaching about 5nm at the level of the duodenal crossing, with mild proximal dilatation of the duodenum and a moderately attenuated third part of the duodenum (Figure 1). Sagittal reformatted images revealed an acute aortomesenteric angle of approximately 23°.

Conservative medical management was adopted, and comprised positioning, gradual feeding and proton pump inhibitors. Additionally, a weight gain

FIGURE 1 Reduced aortomesenteric distance, reaching about 5mm at the level of the duodenal crossing, with a moderately attenuated third part of the duodenum and mild proximal dilatation of the duodenum.

FIGURE 2 Sagittal reformatted multislice CT with oral and intravenous contrast revealed that the SMA had an acute aortomesenteric angle of approximately 23°.
diet was planned. The patient’s condition gradually improved, especially after positioning and hyperalimentation. Ten days after admission the patient was discharged in a good condition. During follow-up visits in the outpatient clinic she was doing well, compliant with medical management and had started to gain weight.

Discussion

Superior mesenteric artery syndrome is an uncommon but well-recognized clinical entity, seen more commonly in females, and usually occurring in older children and adolescents. The incidence of SMA syndrome is about 0.1–0.3%. Approximately 0.013–0.78% of barium upper gastrointestinal radiographs evaluating SMA syndrome support the diagnosis, making it one of the rarest gastrointestinal disorders known to medical science.

Superior mesenteric artery syndrome is favoured by particular anatomical conditions, such as a short or hypertrophic ligament of Treitz, a low origin of the SMA, intestinal malrotation, lumbar hyperlordosis and undernutrition or rapid weight loss leading to reduced thickness of the adipose tissue in the aortomesenteric space. Many causes have been identified, including eating disorders (e.g. anorexia nervosa, malabsorption), conditions leading to cachexia (e.g. neoplasia, acquired immunodeficiency syndrome), situations of hypercatabolism (e.g. multiple trauma, burn victims) and surgical causes such as bariatric surgery or correction of spinal malformation. Other reported causes include accelerated growth in adolescents with a rapid increase in height without weight gain or aneurysm of the abdominal aorta. The anatomical condition leads to a vicious cycle of nausea and vomiting, preventing adequate food intake, which in turn favours weight loss and aggravation of the syndrome.

Patients often present with chronic upper abdominal symptoms, such as epigastric pain, extreme ‘stabbing’ postprandial abdominal pain (as a result of both the duodenal compression and the compensatory reversed peristalsis), nausea, eructation, copious vomiting (bilious or partially digested food), postprandial discomfort, early satiety and sometimes subacute small bowel obstruction. However, our patient had experienced frequent attacks of abdominal pain over several years, which were treated symptomatically and without a clear diagnosis until she presented to our hospital with a clinical picture of subacute small bowel obstruction, which prompted our further investigations.

Diagnosis is very difficult and is usually by exclusion. SMA syndrome is, thus, considered only after patients have undergone extensive evaluation of their gastrointestinal tract, including upper endoscopy, colonoscopy and evaluation for various malabsorptive, ulcerative and inflammatory intestinal conditions with a higher diagnostic frequency. Diagnosis may follow radiological examination revealing duodenal dilatation followed by abrupt constriction proximal to the overlying SMA, as well as a delay in transit of 4–6 hours through the gastroduodenal region. Standard diagnostic examinations include abdominal CT with oral and i.v. contrast and upper gastrointestinal oral contrast with follow-through series. Furthermore, vascular imaging studies, such as Doppler ultrasound and contrast angiography, may be used to identify increased blood flow velocity through the SMA or a narrowed SMA angle. Measuring the aortomesenteric distance and angle is the gold standard in the diagnosis of SMA syndrome.

Plain radiographs revealed a dilated, fluid- and gas-filled stomach, while barium radiography revealed dilatation of the first and second parts of the duodenum, extrinsic compression of the third part of the duodenum and a collapsed small bowel distal to the crossing of the SMA.

Computerized tomography angiography or magnetic resonance angiography enables visualization of vascular compression of the duodenum and precise measurement of aortomesenteric distance and angle. Normally, the aortomesenteric angle and aortomesenteric distance are 38–56° and 10–20mm, respectively, whereas in SMA syndrome both parameters are reduced.

Abdominal ultrasonography may be helpful in measuring the angle of the superior mesenteric artery and the aortomesenteric distance. When combined with endoscopy, it may offer an alternative way to diagnose SMA syndrome in children to avoid other tests with a risk of radiation exposure.

Our patient was referred for radiological assessment and an upper gastrointestinal water-soluble contrast study with follow-through; however, as a result of persistent vomiting despite antiemetic drugs, the examination was cancelled and post-intravenous,
oral contrast, multislice abdominal CT was undertaken instead; this revealed a reduced aortomesenteric artery distance, reaching about 5mm (see Figure 1). Sagittal reformatted images revealed an acute aortomesenteric angle of about 23°, whereas the SMA normally forms an angle of approximately 45° (see Figure 2).

A delay in the diagnosis of SMA syndrome can result in fatal catabolism (advanced malnutrition), dehydration, electrolyte abnormalities, gastric pneumatosis and portal venous gas, aspiration pneumonia, formation of an obstructing duodenal bezoar, hypovolaemia secondary to massive gastrointestinal haemorrhage, gastric distension, and death secondary to gastric perforation or sudden cardiovascular collapse. Although research establishing an official mortality rate may not exist, two recent studies of SMA syndrome patients – one published in 2006 looking at 22 cases and one in 2012 looking at 80 cases – report mortality rates of 0% and 6.3%. The outcome of treatment is generally expected to be excellent.

At least 70% of cases of SMA syndrome can be treated medically. Therefore, medical treatment should be attempted first in all cases, unless emergency surgery is necessary upon presentation. A 6-week trial of medical treatment is recommended in most paediatric cases.

The goal of medical treatment for SMA syndrome is resolution of underlying conditions and weight gain. Medical treatment may involve nasogastric tube placement for duodenal and gastric decompression, mobilization into the prone or left lateral decubitus position, the reversal or removal of the precipitating factor with proper nutrition and replacement of fluid and electrolytes through a surgically inserted jejunal feeding tube, nasogastric intubation or peripherally inserted central catheter administering total parenteral nutrition. Symptoms typically improve after weight gain, unless reverse peristalsis persists, or if fat refuses to accumulate within the mesenteric angle. Most patients seem to benefit from nutritional support with hyperalimentation irrespective of disease history.

The symptoms are typically relieved when the patient is in the left lateral decubitus, prone or knee-to-chest position, and they are often aggravated when the patient is in the supine position. These manoeuvres are thought to reduce the small bowel mesenteric tension at the aortomesenteric angle.

If medical treatment fails, or is not feasible because of severe illness, surgical intervention is required. The most common operation for SMA syndrome, duodenojejunostomy, was first proposed in 1907 by Bloodgood. Performed either as open surgery or laparoscopically, less common surgical treatments for SMA syndrome include Roux-en-Y duodenojejunostomy, gastrojejunostomy, anterior transposition of the third portion of the duodenum, intestinal derotation, division of the ligament of Treitz (Strong’s operation) and transposition of the SMA.

The possible persistence of symptoms after surgical bypass can be traced to the remaining prominence of reverse peristalsis in contrast to direct peristalsis, although the precipitating factor (the duodenal compression) has been bypassed or relieved. Reverse peristalsis has been shown to respond to duodenal circular drainage; a complex and invasive open surgical procedure originally implemented and performed in China.

With such conservative procedures, the condition of our patient gradually improved, especially after positioning. The patient was discharged in good condition with appropriate follow-up and recommendations.

Conclusion

Superior mesenteric artery syndrome, although uncommon, deserves consideration in any patient presenting with chronic upper abdominal symptoms, such as epigastric pain, nausea, voluminous vomiting, postprandial discomfort, early satiety or subacute small bowel obstruction. An upper gastrointestinal contrast study is invaluable in evaluating patients with billious vomiting without abdominal distension and without clear diagnosis; CT with intravenous contrast is a very good alternative when oral contrast is not tolerated.

Finally, the collaboration and case discussion between the different specialties including radiologists, paediatricians, gastroenterologists and surgeons is the key of solving confusing cases when the diagnosis is vague and not straightforward.
References

CASE REPORT

Localized leishmaniasis of the pharyngeal mucosa in the United Arab Emirates

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Abstract

We present a case of mucosal leishmaniasis located in the pharynx and possibly the maxillary sinus in a healthy 51-year-old man. The only manifestations of leishmaniasis disease in the described case were dysphagia, voice changes and a longstanding painless pharyngeal mass. Thorough clinical examination and investigations were carried out and treatment was provided in the form of amphotericin B, piperacillin/tazobactam and linezolid. A review of the literature on this subject has been undertaken.

Background

In most cases, mucosal leishmaniasis occurs as a consequence of cutaneous leishmaniasis. Here we present a case of leishmaniasis exclusively involving the pharyngeal mucosa but with possible paranasal sinus involvement, which is very rare. It was diagnosed in the United Arab Emirates (UAE), which is a non-endemic country, in an immunocompetent patient from Somalia, which is an endemic country for visceral leishmaniasis. We discuss the clinical presentation, diagnostic process and treatment for this patient.

Case presentation

A 51-year-old Somali man presented with the chief complaint of progressive dysphagia and a 2-year history of voice change but no known comorbidities. His medical history included chronic abdominal pain 1 month previously and gradual weight loss over the previous 6 months. His personal history revealed that he was neither a smoker nor an alcoholic; he denied any extramarital sexual relations or intravenous drug use, he had lived in Dubai for 20 years with no recent history of travel and was a driver by profession.

General examination revealed enlarged, tender right cervical lymph nodes, poor oral hygiene and no lesions/scars on the skin of his face, trunks or extremities, nor was there any history of a cutaneous lesion. His abdomen was soft with a palpable spleen. Flexible nasopharyngolaryngoscopy showed a nasopharyngeal mass extending to the orohypopharynx and saliva pooling in the pyriform fossa (Figures 1 and 2).

The patient’s routine blood investigations revealed a normal full blood count, and elevated C-reactive protein (CRP) and erythrocyte sedimentation rate (ESR); viral markers, that is, human immunodeficiency virus (HIV), hepatitis B virus serum antigen and hepatitis C virus, were non-reactive. Computerized

FIGURE 1 Flexible nasopharyngolaryngoscopy showing a nasopharyngeal mass. M, mass; SP, soft palate; TT, torus tubarius.
tomography (CT) of the naso-oropharynx showed a soft tissue mass involving the naso- and oropharynx, enlarged cervical lymph nodes, diffuse soft tissue filling the right maxillary sinus and bone erosion in its inferior wall (Figures 3–6). CT of the chest showed enlarged mediastinal and hilar lymph nodes, and bilateral apical fibronodular infiltrates; CT of the abdomen showed splenomegaly. Panendoscopy was performed and showed a soft tissue mass in the nasopharynx extending through the lateral pharyngeal walls to the oro- and hypopharynx; the vocal cords and oesophagus were normal.

Biopsies were taken from suspicious areas. A histology report revealed chronic inflammation with fibrosis and epithelial hyperplasia, but no evidence of an invasive malignancy. The patient was treated with oral antibiotics and discharged after his symptoms improved. Seven months later the patient returned complaining of the same symptoms of dysphagia and hoarseness. Examination revealed the same findings – a mass in the nasopharynx extending to the oropharynx and hypopharynx. Panendoscopy was
performed and biopsies were taken from suspicious areas. Histology revealed chronic inflammation caused by predominantly lymphohistiocytic granulomas; no vasculitis, necrosis, fungi, parasites or micro-organisms were identified, and there was no definite evidence of malignancy. No specific pathological diagnosis was recognized as the symptoms were non-specific. The patient was again treated with intravenous antibiotics and was discharged following good improvement.

The patient was admitted to our department 8 months later with poor oral intake as a result of worsening dysphagia; examination showed the same mass in the nasopharynx extending to oropharynx and hypopharynx. The results of blood investigations revealed:

- anaemia (haemoglobin 8g/dl)
- white blood cell count 2000cells/ml (leucopenia)
- platelets 65,000cells/ml
- ESR 53mm/h
- CRP 83mg/dl
- the presence of meticillin-resistant Staphylococcus aureus
- normal liver function tests, urea and electrolytes, and thyroid function tests
- cytomegalovirus DNA polymerase chain reaction (PCR) and the Treponema pallidum haemagglutination assay were negative
- non-reactive VDRL (Venereal Disease Research Laboratory) test

- non-reactive T-spot tuberculosis test
- the absence of any pathogen in an acid-fast bacilli smear and culture.

Computerized tomography of the pharynx showed that the mass had increased in volume, extending from the nasopharynx to the hypopharynx with the same findings in the right maxillary sinus. Biopsies were taken from the suspicious areas by panendoscopy. The overall histomorphological features of the biopsies were suggestive of leishmaniasis, with the presence of Donovan bodies and Giemsa stains showing numerous Leishmania amastigotes with eccentric kinetoplasts filling the cytoplasm of the macrophages/histiocytes (Figure 7). We could not confirm the right maxillary sinus involvement by leishmaniasis disease because the patient refused further sinonasal endoscopy and biopsy. He was referred to an infectious diseases unit and was treated for pharyngeal leishmaniasis with amphotericin B, piperacillin/tazobactam and linezolid with good improvement, a decrease in the size of the mass and patent airways.

However, flexible nasolaryngoscopy showed a new involvement of the vocal cords, predominantly on the left side, and possible disease involvement in the left sinus of Morgagni (Figure 8). Further CT of the chest, abdomen and pelvis showed possible diffuse splenomegaly and lung changes suggesting granulomatous disease. Abdomen ultrasound revealed a coarse liver with an irregular outline (suggesting underlying chronic liver disease), a bulky spleen and increased echo texture of both kidneys. The Leishmania antibodies titre was positive at 1:256.
The patient refused further investigations despite hepatosplenomegaly and the pulmonary changes seen on the most recent CT scan, either because of a shortage of money or because he felt better after his initial therapy; however, the possibility of leishmaniasis in other sites could not be ruled out, especially after the positive Leishmania antibodies titre, which is primarily supportive of the presence of visceral leishmaniasis. He was discharged at his request after completion of treatment with significant improvement and given follow-up appointment with the infectious diseases clinic for laboratory investigations and abdomen ultrasound, an appointment with the ear, nose and throat clinic to reassess the new findings in the vocal cords and an appointment with the maxillofacial clinic for a paranasal sinus CT scan.

Discussion

Leishmaniasis is caused by a Leishmania, a protozoan parasite of which there are more than 20 species, and which is transmitted to humans by the bite of infected female Phlebotominae sandflies. According to recent reports and Global Health Observatory data, leishmaniasis is endemic to more than 98 countries and territories. It is estimated that approximately 1.3 million new cases and 20000–30000 deaths occur annually. Leishmaniasis causes significant morbidity and mortality worldwide and its incidence has increased in recent years because of the growing number of patients with immune depression secondary to chronic illness, neoplasm, transplants and HIV infection, thereby constituting a public health problem.

In humans, there are three possible clinical forms of leishmaniasis: cutaneous, mucosal and visceral. However, mucosal and skin lesions may be noted concomitantly, which is known as mucocutaneous leishmaniasis. The term mucosal leishmaniasis traditionally refers to the metastatic sequelae of American cutaneous leishmaniasis, which results from the dissemination of parasites from the skin to mucous membranes of the upper respiratory tract, with lesions mainly in the nasal and oral mucosa and occasionally in the pharyngeal and laryngeal tissue, weeks or decades after the appearance of primary skin lesions. Some patients may also have subclinical skin lesions.

Our patient reported no previous cutaneous lesions or immunosuppression. Thus, a diagnosis of localized leishmaniasis of the pharyngeal mucosa was established. However, mucosal involvement may be the first and only documentable pathological condition due to Leishmania. As a result of its heterogeneous presentation, mucosal leishmaniasis is often misdiagnosed and underestimated by clinicians and scientists, especially in the UAE, which is considered by the World Health Organization a non-endemic country as no any case of any type of leishmaniasis had been reported in the UAE up to the end of 2013.

Diagnosis of leishmaniasis is based on endemicity, clinical symptoms and laboratory test results. In isolated pharyngeal leishmaniasis, the symptoms and pharyngeal lesions are not specific; in fact, they may mimic many inflammatory and neoplastic diseases. Diagnosis is usually further complicated by the absence of any documented history of cutaneous leishmaniasis, as in our case. Furthermore, considering the low incidence of this atypical localization, pharyngeal leishmaniasis is rarely suggested in differential diagnoses by physicians. Confirmation of suspected leishmaniasis requires laboratory tests. Histological evaluation of biopsies is usually able to confirm diagnosis, although it sometimes fails, as in our case, to detect Leishmania amastigotes. For this reason, physicians should inform the pathologist performing the histological examination about their suspicion so that samples can be stained with Giemsa’s stain; the presence of Leishman–Donovan bodies provides histological confirmation of the diagnosis. Other examinations (e.g. leishmanin skin tests and the detection of anti-Leishmania antibodies) can only support diagnosis but PCR is a highly sensitive and specific.
molecular method of detecting the presence of *Leishmania* DNA and identifying the species.

The treatment approach for leishmaniasis depends, in part, on host and parasite factors. Some approaches and regimens are effective only against certain *Leishmania* species/strains and only in particular geographic regions. Pentavalent antimonial (Sbv) compounds such as sodium stibogluconate (Pentostam®, GlaxoSmithKline, London, UK) are the traditional mainstays in the treatment of leishmaniasis. Liposomal amphotericin B and miltefosine are also approved by the US Food and Drug Administration.17

Why did our patient exhibit isolated mucosal manifestations of leishmaniasis? Might this in fact represent secondary localization of the disease as a result of parasites in a dormant site elsewhere? The answer to these questions would be useful in reference to our patient, in whom the most recent CT demonstrated hepatosplenomegaly and pulmonary changes, which might be manifestations of visceral leishmaniasis, and who was positive for *Leishmania* antibodies. This is important because our patient is from Somalia, a country where, according to the World Health Organization, visceral leishmaniasis is endemic, so further investigations should be performed.18 Furthermore, a significant number of cases of visceral leishmaniasis have been reported among travellers in recent years.19,20 Camargo et al.21 discuss the clinical and CT features of 26 patients with mucosal leishmaniasis with involvement of the paranasal sinuses. The involvement of the maxillary sinus is often secondary to involvement of the lateral wall of the nose, which leads to blockage of the ostiomeatal complex. The soft-tissue thickening in the region of the right inferior and middle turbinates, and blockage of the middle meatal region seen on CT in our patient, might also point towards the likelihood of a similar pathogenesis.21

**Conclusion**

Leishmaniasis is rare in our country, and this is possibly the first case of its kind. It shows that physicians, when encountering a patient with the unusual presentation seen in our case, especially someone who has recently arrived from an endemic country, should have a high index of suspicion for leishmaniasis despite it being a rare disease. Ear, nose and throat doctors should remember this rare disease in the differential diagnosis of mucosal lesions to avoid an incorrect diagnosis and prevent inappropriate treatment. More research is needed to discover the mechanisms behind immunity to *Leishmania* in order to explain how pharyngeal leishmaniasis may occur, even in the absence of immune-compromising risk factors.

**References**

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CASE REPORT


Ovarian mucinous cystadenoma arising from a mature cystic teratoma – a case report

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Background

Histologically distinct tumours sometimes coexist in the same organ and are described as collision tumours. Collision tumours involving the ovaries are infrequently reported. In this case we report the coexistence of a mucinous cystadenoma with a mature cystic teratoma of the ovary, the tumour occupying the whole pelvis and abdomen and weighing 10.35kg.

Introduction

Mature cystic teratomas of the ovary, commonly called dermoid cysts, are among the most common benign neoplasms of the ovary and are derived from germ cells. They most commonly occur in young patients, usually during the reproductive years.¹ Ovarian mucinous cystadenoma is a benign tumour that arises from the surface epithelium of the ovary. It is a multilocular cyst with smooth outer and inner surface, and tends to be large. Mucinous tumours constitute 15% of all ovarian tumours.²³ Mucinous cystadenomas are common in those aged 30–50 years.⁴

The coexistence of two adjacent but histologically distinct tumours without histological admixture in the same tissue or organ is rare condition called a collision tumour. The association of a mucinous cystadenoma with a mature cystic teratoma is infrequently reported. Here we report the case of a large ovarian mucinous cystadenoma associated with a mature cystic teratoma weighing 10.35kg.

Case presentation

A 26-year-old unmarried Arabian woman presented to the gynaecological outpatient clinic in Saqr Hospital, Ras al-Khaimah, United Arab Emirates, with abdominal distension over a 1.5-year period associated with loss of appetite. Her menstrual cycles were regular and her weight on presentation was 59kg. During the physical examination, the abdomen looked massively distended with an abdominal mass reaching the xiphisternum. Ultrasonography revealed a multiseptated cystic mass occupying almost the whole pelvis and abdomen (37×23cm), displacing the uterus and causing bilateral hydronephrosis that was more severe in the right kidney, which showed hydrourerter. Other abdominal organs were normal; no free fluid collection could be seen.

Magnetic resonance imaging revealed a 33×20cm benign, multilocular cystic mass with heterogeneous signal intensity, most likely of mucinous origin. This mass affected both kidneys, but predominantly the right kidney, which showed severe hydronephrosis. Tumour markers were as follows: CA-125 70 units/ml (normally 0–35 units/ml); carcinoembryonic antigen 7.60 mg/ml (normally 0.0–4.7 mg/ml); alpha-fetoprotein 3.71 mg/ml (normally 0.0–7.02 mg/ml); and human chorionic gonadotropin 0.1 miu/ml (normally 0.0–3.00 miu/ml).
The patient was admitted for exploratory laparotomy. A midline incision extending 5cm above the umbilicus exposed a huge mass extending from the right ovary, filling both flanks and pushing the diaphragm upwards; the uterus was normal in size but pushed to left side and the left ovary was normal in shape and size. A peritoneal wash with normal saline was performed and the aspirated fluid sent for cytological examination. After packing the abdomen, the cyst was aspirated to reduce its size so that it can be removed through the abdominal incision; approximately 6l of viscous fluid was aspirated before the cyst could be delivered from the abdominal incision.

Right salpingo-oophorectomy was performed as no apparently normal residual ovarian tissue was seen because of the huge size of the cyst. The cyst’s net weight together with the fluid aspirated was 10.35kg. The postoperative period was uneventful and the patient was discharged after 3 days, in good general condition.

Histopathology showed a multiloculated mucinous cystadenoma (28cm in diameter) (Figures 1 and 2), filled with mucin and lined by mucinous epithelium, arising from a mature cystic teratoma (6cm in diameter) (Figure 3), filled with greasy material and hair shafts, and lined by stratified squamous epithelium and skin appendages.

Cytology of the viscous fluid aspirated from the cystic lesion was not specific, showing scattered benign epithelial cells, macrophages and naked nuclei against a background of amorphous mucinous eosinophilic material with no atypical or malignant cells identified. The peritoneal wash revealed no malignant cells.

**Discussion**

Mature cystic teratomas of the ovary are among the most common benign neoplasms of the ovary derived from germ cells, and are commonly seen in young women of reproductive age; the histology of these tumours reveals tissues originating from the ectoderm, mesoderm and endoderm. Mucinous tumours are multiloculated cysts lined by epithelium resembling that of the endocervix. Mucinous cystadenomas account for 8–10% of all epithelial ovarian tumours and
15% of all ovarian tumours;\textsuperscript{2,3} they are bilateral in 10% of cases.\textsuperscript{5}

The coexistence of two distinct tumours in the same organ without any histological intermixing is called a collision tumour.\textsuperscript{6} Collision tumours have been reported in various organs (e.g. the gastrointestinal tract, lung, skin, adrenal glands, central nervous system, lymph nodes, uterus, etc.) but are relatively rare in the ovary. The most common histological combination of collision tumour in the ovary is the coexistence of a teratoma with mucinous tumours.\textsuperscript{7,8}

Various hypotheses have been suggested regarding the formation of collision tumours. The first hypothesis is that the coexistence of two primary tumours in the same tissue is the result of a chance accidental meeting. The second hypothesis proposed is that the presence of the first tumour creates changes in the microenvironment, engendering the development of the second primary tumour or the seeding of metastatic tumour cells. The third theory proposes that each primary tumour has its origins in a common stem cell.\textsuperscript{9}

We present this case in view of the large cyst removed, which occupied the whole abdomen and pelvis, weighed 10.3 kg and caused pressure symptoms on the bowel and renal system. To the best of our knowledge this is the first reported case of such a large collision tumour of the ovary.

\begin{thebibliography}{99}
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CASE REPORT

Peritoneal cyst arising from falciform ligament of the liver

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Abstract

Cysts of the falciform ligament of the liver are rare. To date there have been only 12 reported cases, including the case reported here. In each case, diagnosis was made surgically after the patient complained of pain in the right upper quadrant of the abdomen or following palpation of a mass. We report the diagnosis of a falciform cyst following sonography, computerized tomography, magnetic resonance imaging and exploratory laparoscopy. The cyst was laparoscopically excised (see video clip).

Introduction

The first case of a cyst of the falciform ligament of the liver was reported by Henderson in 1909,1 and there have been a total of 12 reported cases (Table 1), including this one.2

Anatomically, the falciform ligament contains the ligamentum teres hepatitis (the round ligament of the liver), which is the obliterated fetal left umbilical vein. This lies in the free edge of the falciform ligament and extends from the umbilicus to the porta hepatitis, where it attaches to the ligamentum venosum between the two lobes of the liver (Figure 1). The falciform ligament represents a portion of the persistent ventral mesentery consisting of the round ligament, paraumbilical veins, adipose tissue, and a small collection of both smooth and striated muscle fibres.3

Case report

A 30-year-old woman with a history of abdominal pain (lasting a few months) presented with a well-defined epigastric mass in the right upper quadrant. The palpated mass was tense but not tender, extended laterally from the midline of the abdomen, occupied the whole epigastrium and measured 8 × 6 cm. Abdominal ultrasound, computerized tomography (CT) and magnetic resonance imaging (MRI) revealed a large, fluid-filled, well-circumscribed cystic mass (Figures 2–4). During laparoscopy, the lesion was seen to be unilocular, occupied the suprahepatic space, extended to the umbilicus and was attached to the teres ligament (Figure 5). It had a thick fibrous wall and was filled with serous fluid (Figure 6). Histology revealed a benign fibrous lesion lined with one layer of cuboidal epithelial cells (Figure 7). Cytology of the aspirated fluid revealed a proteinaceous background, a few foamy cells and no inflammatory or malignant cells.4

Clinical features, diagnosis and treatment of falciform ligament cyst

As illustrated by the reported cases, symptoms vary individually and present no specific symptom complex. A mass, if noticed, may be the only complaint. Indigestion, flatulence and a feeling of fullness after meals are often symptoms. The pain, when present, often relates to position and varies from a dull, aching, intermittent pain to a sharp, colicky pain that is poorly localized. There are often no physical signs except the presence of a mass. Typically, the mass is tender, lies to the right of the
### TABLE 1 Cases reported in the literature

<table>
<thead>
<tr>
<th>Author(s) and year of publication</th>
<th>Age and sex of patient</th>
<th>Presenting symptoms</th>
<th>Description of falciform cyst</th>
</tr>
</thead>
<tbody>
<tr>
<td>Henderson, 1909</td>
<td>41 years, male</td>
<td>8-year history of abdominal mass</td>
<td>Straw-coloured, thin-walled cystic tumour the size of an infant’s head; unilocular cyst, 8 cm in length, containing clear liquid</td>
</tr>
<tr>
<td>Chifoliau, 1926</td>
<td>49 years, male</td>
<td>4-year history of abdominal mass</td>
<td>Fibrous-walled cyst, 2 inches in diameter</td>
</tr>
<tr>
<td>Wakeley and MacMyn, 1937</td>
<td>54 years, female</td>
<td>Dyspepsia for many years and a 4-month history of abdominal mass</td>
<td>Unilocular cyst the size of an infant’s head</td>
</tr>
<tr>
<td>Herrou, 1937</td>
<td>32 years, male</td>
<td>2-year history of abdominal mass and dyspepsia</td>
<td>Multilocular cyst the size of an infant’s head, with pedicle attached to the liver and umbilicus</td>
</tr>
<tr>
<td>Herrou, 1937</td>
<td>31 years, female</td>
<td>8-year history of right lumbar pain</td>
<td>Mass similar in size to liver</td>
</tr>
<tr>
<td>Lightwood and Campbell, 1939</td>
<td>4 months, male</td>
<td>Abdominal mass from birth</td>
<td>10 × 12 cm cyst with partial torsion around a fibrous band anchored to the anterior abdominal wall</td>
</tr>
<tr>
<td>Brown, 1948</td>
<td>26 years, male</td>
<td>Acute abdominal pain and abdominal mass</td>
<td>Fusiform cyst 6 inches in length, 2 inches in width and 7 inches in depth, filled with sero-sanguinous fluid</td>
</tr>
<tr>
<td>Karabin, 1951</td>
<td>24 years, female</td>
<td>Dull abdominal pain for 6 weeks after blunt trauma to the abdomen; repair of partial eversion of the intestine through the umbilicus at birth</td>
<td>Pear-shaped cyst 9 cm in width, 11 cm in length and 7 cm in depth, reddish brown, containing blood clot and bile-coloured fluid</td>
</tr>
<tr>
<td>Gondring, 1964</td>
<td>27 years, female</td>
<td>6-year history of progressive colicky epigastric pain; abdominal mass</td>
<td>Abdominal/pelvic CT showed 5 cm cystic lesion of the falciform ligament; excised surgically</td>
</tr>
<tr>
<td>Entenime, 1984</td>
<td>27 years, female</td>
<td>11-month history of intermittent abdominal pain; physical examination clear</td>
<td>CT showed large cystic structure in right side of the epigastrum; excised during open surgery</td>
</tr>
<tr>
<td>Patel, 2009</td>
<td>61 years, female</td>
<td>12-month history of abdominal pain and bloating</td>
<td>Sonography, CT, magnetic resonance imaging and exploratory laparoscopy revealed 8 × 6 cm cyst</td>
</tr>
<tr>
<td>Al-Judi and Safarini, 2017</td>
<td>30 years, female</td>
<td>Upper abdominal pain and epigastric mass</td>
<td>CT, computed tomography.</td>
</tr>
</tbody>
</table>

**FIGURE 1** The falciform ligament in relation to the parietal peritoneum, round ligament and liver lobes.

**FIGURE 2** Abdominal ultrasound scan showing the cyst occupying the epigastric region on both sides (left/right) and the central attachment to the linea alba (arrow).
midline, does not extend below the umbilicus and does not move with breathing.

A striking similarity between the previous 11 cases is the mistaken assumption that a tumour in the right upper quadrant is a renal, hepatic or gall bladder tumour. Pertinent history, physical signs and imaging modalities (sonography, CT and MRI) are of value for ruling out the extensive list of differential diagnoses for a lesion in this area of the body.
Treatment is laparotomy, for which the correct procedure is to excise the cyst to obtain the correct pathological diagnosis and to avoid subsequent complications such as haemorrhage, infection, twisting (if the cyst is attached to a pedicle or a fibrous band is present), torsion and strangulation. In this case, laparoscopy included the excision of the cyst (see video clip). There were no operative or post-operative complications.

Discussion

The patient was asymptomatic from birth until the cyst grew large enough to be palpable and painful, causing a noticeable increase in abdominal size. MRI can be helpful in revealing the size, content and boundaries of a cyst, but cannot define the nature or origin of the cyst or rule out malignancy. T2 MRI showed the fixed tenting point of the anterior border of the cyst at the umbilicus along the midline of the epigastric area. This may be a newly identified indication that the cyst arises from the falciform ligament of the liver, which could allow preoperative diagnoses in future cases (see Figures 1–3).

Conclusion

A cyst of the falciform ligament is another entity to consider in the differential diagnosis of a mass in the right upper quadrant that may be attached to the anterior abdominal wall towards the midline and above the umbilicus. Available imaging modalities – sonography, CT and MRI – can aid diagnosis of these rare cysts. Nevertheless, the only currently available option for diagnosis and treatment is laparotomy.

References

Severe aortic coarctation incidentally discovered in a young university student

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Abstract
Coarctation of the aorta is a narrowing of the descending aorta, resulting in left ventricular overload, arterial hypertension and cardiovascular and neurological complications. It is frequently diagnosed in infancy and childhood; first-time presentation in adults is rare. The classic symptom is arterial hypertension; most patients are asymptomatic unless hypertension is present. We report the case of a 19-year-old woman who presented with a headache, tiredness and arterial hypertension. Clinical examination revealed that blood pressure was significantly lower in the lower extremities than in the upper extremities and radiofemoral delay (delayed femoral pulses). Severe aortic coarctation was confirmed by computerized tomography aortography; echocardiography was inconclusive. The lesion was successfully treated with balloon dilatation and mesh stent placement.

Introduction
Coarctation of the aorta accounts for 5–10% of all congenital heart defects. Most cases are sporadic, with a reported prevalence of about 1 in 10000 live births. It occurs more frequently in men than in women (59% vs. 41%, respectively). There are two theories regarding its cause: one attributes coarctation of the aorta to reduced anterograde intrauterine blood flow, causing underdevelopment of the fetal aortic arch, the other to migration or extension of the ductal tissue into the wall of the fetal thoracic aorta. The defect results in left ventricular overload, arterial hypertension, heart failure, neurovascular complications such as stroke and intracranial aneurysms.

Case report
A 19-year-old female university student presented with headaches, tiredness and incidentally discovered arterial hypertension which had been ongoing for almost 1 year. Examination revealed a well-built female with tachycardia (with a heart rate of 115 bpm). Her blood pressure was 160/88 mmHg in the left arm and 185/95 mmHg in the right arm. Pulses in the lower extremities were weak and delayed, with a blood pressure of 110/70 mmHg. Cardiac auscultation was unremarkable. Electrocardiography revealed signs of left ventricular hypertrophy. Chest radiography was normal.

Echocardiography revealed signs of mild left ventricular hypertrophy. However, aortic isthmus imaging was inconclusive. As a consequence, computerized tomography (CT) aortography was performed, showing aortic isthmic hypoplasia, rich periscapular and intercostal collaterals, coarctation and the classic reverse-figure 3 (Figure 1). Diagnostic and therapeutic cardiac catheterization was performed; it confirmed the diagnosis of severe aortic coarctation in the thoracic aorta, distal to the origin of the left subclavian artery, with multiple collaterals (Figure 2). Haemodynamics revealed a systolic gradient of about 50 mmHg. The coarctation
area was dilated by balloon, which led to a significant improvement in the haemodynamic results. However, after balloon dilatation, pre-stenotic pressure was 143/70mmHg, whereas post-stenotic pressure was 123/68mmHg. Therefore, a $4.5 \times 16$mm stent was deployed over the balloon, achieving maximum dilatation and producing very good results (Figure 3).

**Discussion**

First-time presentation of aortic coarctation in adults is rare. The average life expectancy of individuals with unaerated coarctation is approximately 35 years; 75% of affected individuals are dead by the age of 46 years. In previously undiagnosed adults, the classic symptom is arterial hypertension; most patients are asymptomatic unless hypertension is present. Aortic coarctation may cause headaches, epistaxis, heart failure or aortic dissection. Our patient presented with a history of hypertension and headaches lasting almost 1 year. The diagnosis was based on systolic hypertension in the upper extremities, radiofemoral delay (delayed femoral pulses) and low blood pressure in the lower extremities.

Electrocardiography in adults may be normal or show signs of left ventricular hypertrophy, as it did in our reported case. In older children and adults, abnormal radiography results are not uncommon, including signs of indentation of the aortic wall at the site of lesion with pre- and post-coarctation dilatation, and notching of the posterior one-third of the third to eighth ribs due to erosion by collateral arteries. However, chest radiography may be normal, as it was in our patient.
Transthoracic echocardiography can establish the diagnosis, assess the gradient across the coarctation and detect associated cardiac defects in most patients. However, the presence of collateral blood flow may diminish the gradient across the coarctation, and it may be less severe than expected considering the degree of obstruction. Adult echocardiography can be technically demanding and both false-negative and false-positive results are frequent. In our case, echocardiography of the cardiac isthmus was difficult and inconclusive. Therefore, the diagnosis was confirmed by multislice chest CT aortography. Furthermore, the 2008 American College of Cardiology and American Heart Association (ACC/AHA) guidelines recommend that every patient with aortic coarctation, repaired or not, should undergo CT at least once (or magnetic resonance imaging) for complete evaluation of the thoracic aorta.

Although correction of coarctation can sometimes be delayed in children, it should be performed in adults at the time of diagnosis. The 2010 European Society of Cardiology guidelines for management of adult congenital heart disease state that all patients with a non-invasive pressure difference of >20mmHg between upper and lower limbs, regardless of symptoms, but with upper limb hypertension (>140/90mmHg in adults), pathological blood pressure response during exercise or significant left ventricular hypertrophy should undergo the intervention. On the other hand, the 2008 ACC/AHA guidelines for congenital heart disease recommend intervention if the peak-to-peak coarctation gradient is ≥20mmHg, or if the peak-to-peak coarctation gradient is <20mmHg but there is anatomical imaging evidence of significant coarctation and radiological evidence of significant collateral flow. Stent placement after balloon angioplasty has been reported to reduce complications associated with angioplasty or surgery, minimize residual gradient, improve luminal diameter and sustain haemodynamic benefits. Our patient met both European and ACC/AHA criteria for intervention, so she underwent a successful stent placement after balloon angioplasty. Her blood pressure returned to normal and follow-up after 1 year confirmed clinical stability.

Conclusion

Although uncommonly diagnosed in adults, aortic coarctation should not be overlooked as a potential cause of secondary systemic hypertension; careful clinical examination is crucial. All patients with systemic arterial hypertension should undergo clinical examination that includes radial, brachial and femoral pulse palpation. Examining blood pressure in the upper and lower limbs is an essential part of the primary evaluation of patients with systemic hypertension. Diagnostic tests including echocardiography, CT aortography and angiography should be performed to confirm and guide diagnosis and management. Balloon angioplasty and stent placement for aortic coarctation is an evolving procedure, with significant improvements being observed over the past two decades.

References
