Résumé

La formation médicale nécessite d'être optimisée en permanence afin de s'adapter à l'évolution des besoins de la pratique clinique au 21e siècle. Nous devons revoir les méthodes pédagogiques employées, ainsi que le contenu de l'enseignement dispensé lors des diverses étapes de la formation d'un médecin. Les généralistes doivent reconnaître les symptômes révélateurs de la SEP et adresser le patient à un spécialiste. Les neurologues confirment le diagnostic, administrent un traitement et assurent la prise en charge et le soutien du malade. La formation doit être adaptée à la réalité des ces différentes tâches et offrir les outils requis au médecin. Nous proposons un programme de formation à l'attention des étudiants de premier cycle, comprenant trois cours magistraux et deux sessions interactives couvrant les notions fondamentales sur la SEP et sa prise en charge. Pour les étudiants visant une spécialisation en neurologie, nous recommandons une série de huit cours magistraux, des séances interactives incluant des études de cas sur les formes typiques et atypiques de la maladie, deux séances d'interprétation d'IRM avec un neuroradiologue spécialisé, et de l'exercice dans une clinique spécialisée en SEP.

Überblick

Medizinische Ausbildung bedarf ständiger Verbesserungen, um mit der Entwicklung der Anforderungen an die medizinische Praxis im 21. Jahrhundert mitzuhalten. Wir müssen die Lehrmethoden und das Curriculum überdenken, das in den verschiedenen Phasen der medizinischen Ausbildung gelehrt wird. Allgemeinärzte müssen die für MS indikativen Symptome erkennen und den Patienten an einen Spezialisten überweisen. Neurologen bestätigen die Diagnose und bieten dem Patienten wirksame Behandlungsmethoden und Unterstützung. Die Ausbildung muss so angepasst werden, dass diese verschiedenen Aufgaben berücksichtigt und Ärzte entsprechend ausgerüstet werden. Wir schlagen ein Schulungsprogramm für Studenten im Grundstudium vor, das aus drei Vorlesungen und zwei interaktiven Kursen besteht. Diese sollen den Studenten das Grundwissen über MS und ihrer Behandlung vermitteln. Für diejenigen, die sich auf Neurologie spezialisieren möchten, empfehlen wir eine Serie von acht Vorlesungen sowie interaktive Kurse, in denen Fallbeispiele mit typischen und atypischen Präsentationen besprochen werden, zwei Kurse, in denen mit einem Spezialisten der Neuroradiologie Magnetresonanztomographieaufnahmen ausgewertet werden sowie die Hospitanz in einer MS-Klinik.

Sommario

La formazione professionale dei medici richiede miglioramenti continui per soddisfare le mutevoli esigenze della prassi medica del XXI secolo. Dobbiamo riesaminare i metodi di insegnamento usati e il curriculum adottato per i vari stadi di formazione professionale dei futuri medici. I medici di prima linea devono riconoscere i sintomi indicativi della SM ed indirizzare il paziente ad uno specialista; i neurologi confermeranno quindi la diagnosi, e tratteranno, gestiranno e supporteranno efficacemente il paziente. La formazione professionale deve essere adattata in modo da riflettere questi compiti diversi, e preparare in maniera conseguente il medico. Suggeriamo un programma di formazione professionale per gli studenti universitari che include tre lezioni e due sessioni interattive. Queste fornirebbero allo studente conoscenze di base sulla SM e sulla sua gestione. Per chi desidera specializzarsi in neurologia, raccomandiamo una serie di otto lezioni e sessioni interattive in cui si discutono rapporti sulla casistica con presentazione tipica ed atipica, due sessioni di lettura di imaging a risonanza magnetica con un neuroradiologo specializzato, ed esperienza attiva in una clinica di SM.

Reseña

La educación médica necesita mejorar continuamente para satisfacer las exigencias de la práctica médica en constante cambio en el siglo 21. Es necesario revisar los métodos de formación y los programas de estudios que se imparten durante las diferentes etapas de la formación de un médico. Los médicos de medicina general deben reconocer los síntomas indicativos de la esclerosis múltiple y remitir el paciente a un especialista. Los neurólogos deberán confirmar el diagnóstico y prescribir con eficacia el tratamiento, el control y la asistencia al paciente. La formación debe estar adaptada con el fin de reflejar las diferentes tareas y equipar al médico debidamente. Nuestra sugerencia es un programa de formación para estudiantes universitarios que conste de tres clases y dos sesiones interactivas. Estas clases y sesiones ofrecerán al estudiante un conocimiento básico de la esclerosis múltiple y su control. Para los estudiantes que deseen especializarse en neurología, recomendamos una serie de ocho clases, sesiones interactivas sobre informes de casos con presentaciones típicas y atípicas, dos sesiones de lectura de imagen de resonancia magnética con un neurorradiólogo y la práctica activa en una clínica de esclerosis múltiple.

サマリー

21世紀の医学教育は医療に対する需要の変化に対応するため、常に進歩し続ける必要がある。我々はこれまでに用いられてきた教育方法や医師育成のさまざまな場面で使用するカリキュラムを見直す必要がある。一般開業医はMSの兆候を 認識し、患者を専門医の元へ送らなくてはならない。専門医、つまり神経科医は診断を確定し、効果的な治療を行い、患者を管理サポートする。これらの異なる役割を反映し、各々の医師にとって必要な知識を身につけられるような教育を取り入れるべきである。我々は3回の講義と2回の対話型セッションで構成される大学生用の教育プログラムを提案する。これらの授業では学生にMSの基礎知識とその対処法を教える。また、神経学を専攻する学生には、8回の講義と典型例及び非典型例の症例報告ついて検討する対話型セッション、神経放射線専門医と行うMRI読影についての2回の授業、そしてMSクリニックでの実務研修からなるコースを推奨する。

Medical Education and MS: Getting the Training Right

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Summary

Medical education needs continuous improvements to meet the changing demands of medical practice in the 21st century. We need to review the teaching methods used and the curriculum taught during various stages of a doctor's training. General practitioners need to recognize the symptoms indicative of MS and refer the patient to a specialist; neurologists should confirm the diagnosis, and effectively treat, manage and support the patient. Training should be adapted to reflect these different tasks and equip the physician accordingly. We suggest a training programme for undergraduate students comprising three lectures and two interactive sessions. These would provide the student with a basic knowledge of MS and its management. For those wishing to specialize in neurology, we recommend a series of eight lectures, interactive sessions discussing case reports with typical and atypical presentations, two magnetic resonance imaging reading sessions with a specialist neuroradiologist and active practice in an MS clinic.

KEY WORDS:

Multiple sclerosis; Medical education; Teaching methods; MS symptoms; MS diagnosis

Introduction

There has been widespread interest recently in revising undergraduate and postgraduate medical training in each speciality area. Medical education needs continuous improvements to meet the changing demands of medical practice in the 21st century.

A basic science segment followed by a period of clinical study and practice characterizes the traditional approach to medical training. This type of training through a lecture-based curriculum has been criticized for several reasons. First, it tends to separate the basic science segment from medical practice too much. Secondly, it requires passive assimilation of information by students. Finally, practicing doctors do not use large parts of the knowledge they acquired as students and the essentials of 'real world' medicine might not be grasped.

Several studies have compared the conventional teaching approach with alternative or complementary methods, including problem-based learning (PBL),[1] small group teaching,[2] bedside teaching,[3] and problem-oriented practical sessions (POP);[4] descriptions of these different techniques are given in Table 1. It is necessary, therefore, to understand how to apply these learning strategies to undergraduate and postgraduate courses in each medical speciality.

In the field of MS, the need to provide courses specifically designed for a particular stage of overall training and chosen speciality is evident. This is not a rare disease, but a general practitioner or family physician rarely sees a patient at the beginning of the illness. It is even more unlikely that they will be consulted during the course of the disease, as the patient will be in the care of a neurologist.

Multiple sclerosis patients occupy the sixth position among neurological diseases seen by a general practitioner in a busy practice; patients with headaches, cerebro-vascular diseases (CVD), vertigo, epilepsy and Parkinson's disease are seen more frequently.[5] General practitioners might see one new MS patient for every thousand medical consultations, but are generally not in charge of diagnosis, treatment or follow-up. It follows, therefore, that general medical training should concentrate on the essentials of patho-physiology, clinical aspects, disease course, common complications and rationale for available treatments. What needs to be remembered is that the main tasks of a general practitioner are to recognize the early

signs and initial complaints indicative of MS, and to refer the patient to a specialist centre without delay.

The training needs for would-be neurologists are different. After epilepsy, CVD, headache and dementia, patients with MS comprised the fifth largest cohort of neurology out-patients 15 years ago.[6] Since then, the number of patients with MS who visit specialists has increased due to improved awareness of the disease and its treatment. The education of physicians practicing neurology must, therefore, be tailored to these advances. Neurologists need a solid clinical expertise so that they can make a correct diagnosis as soon as possible, and initiate early treatments according to the best scientific evidence. The specialist is also required to increase patient and family disease awareness, and to respond to requests for information on prognosis, planning significant life events and the state of research. To equip neurologists with such skills and knowledge, the current postgraduate training curriculum needs revising.

Teaching MS to Medical Students

The best approach to MS education for undergraduates is a series of lectures followed by some practical activity within small groups. The course could comprise three lectures and two interactive sessions; the proposed content is described in the following sections.

Key Points

- *In the field of MS, we need to provide courses specifically designed for general and speciality training*
- *General practitioners need to learn to recognize the early signs and initial complaints indicative of MS and refer the patient to a specialist centre without delay*
- *Neurologists need to make a correct diagnosis as soon as possible and initiate appropriate early treatments*
- *For undergraduates we recommend a series of lectures followed by some practical activity within small groups*
- *We suggest that the postgraduate neurological course in MS should combine interactive sessions discussing case reports, lectures, a reading session on conventional and non-conventional MRI techniques and practical experience in an MS clinic*

Lecture 1: Clinical Presentations

Onset

Illustrate how the beginning of MS is polysymptomatic in 55% of cases and monosymptomatic in 45%.

Table 1: Undergraduate and postgraduate medical training: methods of teaching and learning

Problem-based learning (PBL)	Teaching basic science and clinical disciplines using a combination of group discussions and individual research. Students decide their own learning objectives and strategies; a teacher guides the sessions, promoting thinking, problem solving and encouraging interaction, but does not lecture. Students learn by actively solving clinical problems and making decisions rather than by passively absorbing information. The method uses a problem as the starting point for student learning. Students spend more time in self-learning and make more use of informational resources, such as libraries or computer laboratories. There is evidence that PBL students are better prepared to apply basic science concepts in clinical settings: they retain knowledge over a longer time period and may be better prepared for life-long learning. Students using the conventional model performed better in basic science examinations, however
Small-group teaching	Eight to ten students interact with each other to facilitate active learning by each individual. Their goals are to: learn from each other; be able to ask questions and think things through; apply content to clinical or 'real life' situations; and learn how to solve problems. This method merges with existing learning strategies. It may be difficult for the tutor to accommodate each participant's learning style, however, and some topics requiring simple memorization may not be appropriate for group discussion. This kind of learning needs to be incorporated into the curriculum to provide a good learning experience
Bedside teaching	Very good for understanding and memorization, but limited by the need for the continuous presence of the teacher and the number of available patients covering the entire spectrum of clinical conditions
Problem-oriented practical (POP)	Clinical problems are presented as paper cases with high-quality colour photographs demonstrating the clinical features. This course is not dependent on the availability of real patients

Symptomatology is established, most often, in the acute (hours) or sub-acute (days/weeks) modes. Onset of the disease develops slowly over a period of 6 months or more in only about 10% of cases. The most common symptoms at onset should be covered.

Symptoms

It is useful to underline the following points: the variability of symptoms and signs according to lesion size and distribution, and the extent of inflammation and oedema. Gliosis and axonal loss begin very early in the disease course and are responsible for disability and the progressive course. An accurate description of the most common as well as the less frequent symptoms is given in Table 2.[7]

Table 2: Frequency of symptoms at onset and during the course of MS[7]

Symptoms	At onset (%)	During the course of disease (%)
Visual dysfunction	13	49
Diplopia	8	51
Facial weakness	1	16
Facial pain	2	35
Ataxia	11	82
Dysarthria	0.6	37
Dysphagia	0.3	13
Vertigo	4.3	36
Weakness	22	89
Sensory	34	87
Ageusia	0.3	6
Bladder dysfunction	1	71
Bowel dysfunction	0	42
Cognitive impairment	0.3	32
Fatigue	2	57
Cramps	0.6	52
Headache	2	30
Neuropsychiatric	0.3	23
Blackouts	0.6	11
Other*	1	10

*Including hemiballism, dystonic chorea, choreoathetosis, restless legs syndrome, facial hemispasm.

Disease course

Indicate how the evolution of the disease is characterized by an extreme heterogeneity and how MS is not necessarily a disabling disease. It is appropriate to mention the concept of clinical relapse and the variable disease course. The classifications currently receiving the highest consensus level internationally and their frequency should be discussed.[8] Briefly, relapsing–remitting (RR) MS is characterized by clearly defined acute attacks with full recovery (Figure 1A) or with sequelae and residual deficit upon recovery (Figure 1B); periods between relapses are characterized by lack of disease progression. Disease showing progression of disability from the onset is described as primary progressive (PP) MS, and may occur without plateaus or remissions (Figure 1C) or with occasional plateaus and temporary minor improvements (Figure 1D). Secondary progressive (SP) MS begins with an initial RR course, followed by progression of variable rate (Figure 1E) that may also include occasional relapses and minor remissions (Figure 1F). Progressive–relapsing (PR) MS shows progression from onset, but with clear acute relapses with (Figure 1G) or without (Figure 1H) full recovery.[8]

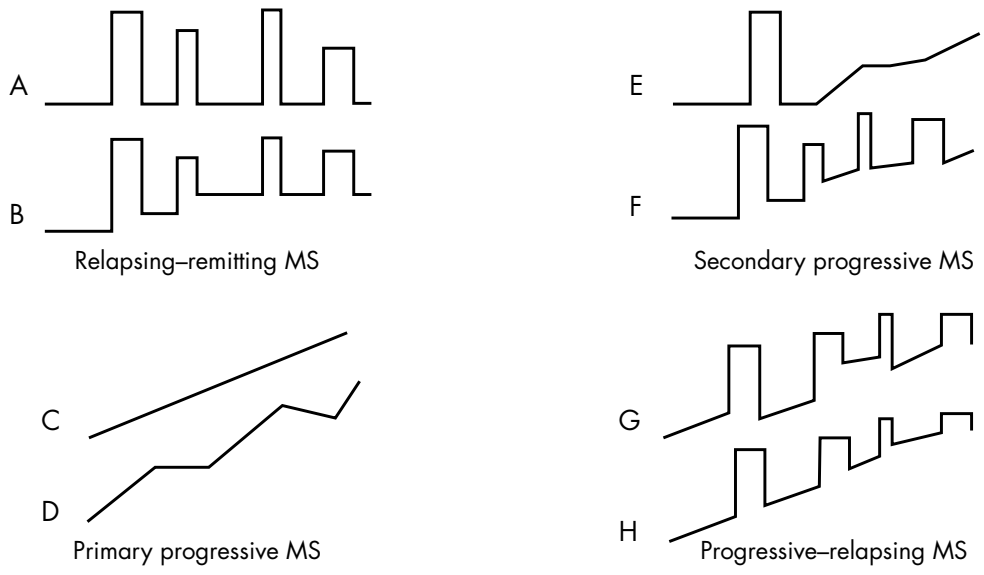

Figure 1. The various clinical patterns of MS (modified from Lublin and Reingold)[8]

Prognostic indicators

Areas to cover include clinical and demographic factors, magnetic resonance imaging (MRI) parameters, and new imaging modalities that show evidence of early axonal loss. Cognitive and mood disorders may be important correlates of neurodegeneration in advanced stages of MS.

Lecture 2: Epidemiology and Pathogenesis of MS

Incidence and prevalence related to age of onset, gender and geographic distribution

Discuss age of onset, sex ratios and geographic distribution.[9] The impact and prevalence of MS varies enormously according to latitude and regional location, and there are distinct zones of high, medium and low impact. For example, clusters of MS occur in Sardinia, and the disease has presented characteristics of MS 'epidemics' on the Faroe Islands and in Iceland. Before World War II, there were no reported cases of MS on the Faroe Islands, however, 46 cases were identified between 1943 and 1982. These data have been interpreted to indicate a point-source epidemic temporally related to the stationing of approximately 8000 British troops on the islands during World War II.[10]

Pathogenesis

Show how MS is a multifactorial disease resulting from an interaction between genetic susceptibility and early exposure to environmental factors. Discuss the studies that identified specific genetic markers associated with MS, such as the HLA DR2 haplotype, and those concerning the relationship between illness course and gene polymorphisms. No clear link has yet been shown between disease course and the existence of genetically protective markers.

Clearly indicate the role of familiar recurrence:[11] the risk of developing MS is 10–20 times higher in relatives of a person with MS than in the general population. Twin studies reveal a prevalence of MS of 20–30% in monozygotic siblings and 2% in dizygotic twins in north European and north American populations. The rates are 8% and 2% respectively in the Italian twin population (Ristori G, personal communication). The results of adoptee and half-sibling studies should also be mentioned. The relative contribution of environmental versus genetic factors in MS should be illustrated using migration studies and by geographic gradients and clusters in ethnically stable populations.

It is appropriate during this lecture to make reference to the auto-immune mechanisms underlying the pathology, and the following should be highlighted: mechanisms underlying the inappropriate immune response to myelin; immune effectors of the auto-aggressive response (lymphocytic T-cells, lymphocytic B-cells and other immunocytes); principal events leading to the complex inflammatory reaction causing demyelination and axonal damage.

In recent years, identifying specific auto-antigens for MS has been a principal research activity and hence warrants a mention. Among the most important candidates are myelin basic protein (MBP), myelin oligodendrocyte glycoprotein (MOG), proteolipid protein (PLP), myelin-associated glycoprotein (MAG) and the protein S100b.

Lecture 3: Diagnosis and Treatment

Diagnostic methods

Explain how the clinical diagnosis is based on two important criteria: spatial and temporal dissemination of the injury. At present, the evolution of neuroradiological techniques allows an earlier and more accurate diagnosis, documenting a higher recurrence rate of demyelinating lesions and of new active lesions using MRI.

It is important to note that there is no unified paraclinical test for diagnosing MS. Achieving the gold standard for diagnosis rests, therefore, with the clinic staff. The roles of cerebrospinal fluid (CSF) and evoked potentials should be discussed, with warnings that neither are MS specific.

Current preventive therapies available, symptomatic treatments and psychological support

In the past 10 years, research aimed at finding therapies to modify the natural course of MS has increased greatly. It is fundamentally important that doctors are aware of such therapies and research and can discuss them with patients to eliminate the idea that MS is incurable. It is useful to underline the following points during the lecture: rationale for and type of anti-inflammatory and symptomatic treatments available; recent advances in research; late disease complications (such as spasticity, spasms, pain, bladder dysfunction or tremor) and their management; and timelines for new therapeutic research.

General physicians should know about the best time to initiate treatment, the role of symptomatic

treatments, use and availability of psychosocial support, rehabilitation and non-professional MS associations. They should not be concerned with the in-depth arguments of published studies.

Interactive Sessions

We suggest two interactive sessions that discuss the presentation of typical and atypical clinical cases and involve a neuroradiologist. The role of the neuroradiologist is to present the most common MRI findings in patients with MS. In addition they should describe the aspects of injury seen throughout the disease course, and their typical multiplicity and distribution in the white matter. Emphasis should be placed on damage localized to the sub-cortical junction, as this is common in MS and useful in the differential diagnosis with sub-cortical atherosclerosis. Similarly, involvement of the corpus callosum is frequent in MS and rare in vascular diseases. The importance of requesting a paramagnetic contrast (gadolinium) examination must also be stressed.

Teaching MS to Neurologists in Training

Multiple sclerosis education during the postgraduate neurological course is most effectively achieved using an intelligent combination of traditional and PBL approaches. The course could start with the exposition and discussion of clinical case reports during interactive sessions. Learning could then be reinforced by formal lectures. We suggest the following four-step course structure: two interactive sessions discussing case reports and involving a neuroradiologist; eight lectures to provide further insight into the field of MS and other demyelinating diseases of the CNS; one or more reading sessions concerning conventional and non-conventional MRI techniques; and practice of diagnosis and therapeutic management with at least three patients.

Interactive Sessions

Discuss case reports illustrating typical and atypical presentations of MS.

Lecture 1: Epidemiology and Clinical Presentation

Epidemiology

A detailed description of the general characteristics of MS should be given, including: the female to male ratio; age of onset; geographical distribution; prevalence and incidence; and genetic and environmental factors.[12]

Clinical aspects

Describe the first episode suggestive of MS, including symptoms and signs and their frequency at onset and during the course of the disease. Clinical patterns of MS, the natural history of MS (as for undergraduate students) and issues concerning MS and pregnancy can also be discussed in this lecture.

Lecture 2: Pathogenesis

The following aspects should be discussed:[13,14]

- How genetic and environmental factors (including viral infection, bacterial lipopolysaccharides, superantigens, reactive metabolites and metabolic stress) may facilitate movement of autoreactive T-cells and demyelinating antibodies from the systemic circulation into the central nervous system (CNS) through disruption of the blood–brain barrier (BBB);
- How local factors in the CNS may up-regulate expression of endothelial adhesion molecules, such as intercellular adhesion molecule 1 (ICAM-1), vascular-cell adhesion molecule 1 (VCAM-1) and E-selectin, further facilitating entry of T-cells into the CNS;
- How proteases, including matrix metalloproteinases, may further enhance migration of autoreactive immune cells by degrading extracellular-matrix macromolecules;
- How pro-inflammatory cytokines released by activated T-cells, such as interferon-γ and tumour necrosis factor β (TNF-β), may up-regulate expression of cell-surface molecules on neighbouring lymphocytes and antigen-presenting cells;
- How binding of putative MS antigens may trigger an enhanced immune response against the bound antigen or anergy, depending on the type of signalling resulting from interactions with surface co-stimulatory molecules (e.g., CD28 and CTLA-4) and their ligands (e.g., B7-1 and B7-2).

The multiple mechanisms of immune-mediated injury of myelin should also be mentioned. These comprise: cytokine-mediated injury of oligodendrocytes and myelin; digestion of surface myelin antigens by macrophages, including binding of antibodies against

myelin and oligodendrocytes (i.e., antibody-dependent cytotoxicity); complement-mediated injury; and direct injury of oligodendrocytes by CD4+ and CD8+ T-cells.

The lecture should also cover the effect of myelin membrane injury on denuded axons that are no longer able to transmit action potentials efficiently within the CNS. These axons are susceptible to further injury from soluble mediators, including cytokines, chemokines, complement and proteases, resulting in irreversible injury (e.g., axonal transection and terminal axon ovoids).

Students also need to be familiar with myelin membrane repair mechanisms. Information on inflammatory response resolution followed by spontaneous remyelination, the spread of sodium channels from the nodes of Ranvier to cover denuded axon segments and restore conduction, antibody-mediated remyelination, and remyelination resulting from proliferation, migration, and differentiation of resident oligodendrocyte precursor cells should be provided, therefore.

Lecture 3: Neuropathological Aspects

Trainee neurologists need to understand in more detail the underlying pathology of MS. This is achieved by explaining how the injury target (myelin or oligodendrocytes) and demyelination mechanisms are distinctly different in subgroups of the disease and at different stages of disease development.[15] Most cases share a common T-cell- and macrophage-dominated inflammatory reaction. From a neuropathological perspective, however, lesions can be segregated into those with close similarities to autoimmune encephalomyelitis (patterns I and II) and those with signs of oligodendrocyte dystrophy (patterns III and IV). Pattern I and II lesions, have a typical perivenous distribution, but seem to have different myelin injury mechanisms. In pattern II lesions, the pronounced deposition of immunoglobulins and complement C9 neoantigen at sites of active demyelination suggest an important role for antibodies, but this has not been detectable in pattern I lesions. Pattern III demyelination is not focused on inflamed blood vessels; the lesion contours are ill-defined, with concentric layering of myelinated and demyelinated tissues and signs of oligodendrocyte dystrophy. Pattern IV lesions, which were exclusively present in a subgroup of patients with PPMS, show similarities with classical pattern I and II lesions. Extensive loss of oligodendrocytes, lack of remyelinated shadow plaques and DNA fragmentation in oligodendrocytes in the periplaque white matter suggest that the oligodendrocytes are impaired in pattern IV lesions, however.

The importance of inflammatory processes in the development of axonal damage, even in the earliest phase of the disease, needs to be underlined.[16] Specifically, this section should cover: how axonal destruction in MS lesions could result from direct immunological attack by soluble inflammatory mediators, or from secondary effects of chronic demyelination; the vulnerability of demyelinated axons to an inflammatory environment; and that proteolytic enzymes, cytokines, oxidative products, and free radicals produced by activated immune and glial cells cause axonal transection. There is also the possibility that chronic demyelination may lead to axonal degeneration, as supported by the finding of terminal axonal ovoids in the centres of chronic active lesions. Myelination provides an extrinsic trophic signal to axons that increases axonal calibre, and the loss of this effect can result in axonal degeneration.

How could axonal injury in MS be responsible for permanent neurological dysfunction once a threshold of axonal transection has passed? This question is investigated by discussing the clinical and therapeutic implications of extensive axonal transection in MS lesions. During the RR-stages of disease, restoring conduction along demyelinated axons, redundant neuronal pathways, or axonal sprouting may compensate for axon destruction. A threshold of axonal loss is eventually reached, however, after which patients experience progressive neurological deterioration that typically occurs in the SP-phase of MS. Major therapeutic and research efforts should be directed towards limiting immune-mediated damage to myelin and axons, and to promoting remyelination, therefore.

Lecture 4: Diagnosis of MS

Diagnostic methods

The 'traditional' diagnostic criteria should be described in this lecture, stressing the clinical hallmark of MS according to the Schumacher criteria:[17] dissemination of clinical episodes in space and time. The increasing role of paraclinical instruments (oligoclonal bands in the CSF, evoked potential and MRI) in diagnosing MS according to the Poser criteria[18] is also important. The need for new diagnostic criteria to allow diagnosis and the initiation of therapy as soon as possible should be underlined. This will also aid the diagnosis of MS in patients with 'monosymptomatic' disease, a typical

relapsing–remitting course, an insidious progression, and in those without clear attacks and remissions. The more recent McDonald criteria[19] need to be discussed, particularly the clinical/paraclinical diagnostic protocol, so that subclinical dissemination in space and time can be determined. Definitions of a 'relapse' and 'disability progression' should also be given.

The neurological clinical scales most frequently used to evaluate different features of MS should be discussed, and their advantages and limits analysed. Scales used include the Expanded Disability Status Scale (EDSS), Scripps Scale, and specific scales for evaluating symptoms (i.e. fatigue and depression) and quality of life.

Differential diagnosis

It is important to teach trainee neurologists how to distinguish MS from other diseases of the CNS that may have similar initial symptoms.[20] This can be achieved by providing clinical examples and by concentrating on the specific criteria defined for each disease. The differential diagnosis may include Sjogren's syndrome, Behçet disease, sarcoidosis, systematic sclerosis, borreliosis, cerebrovascular disease, meningovascular syphilis, acute demyelinating encephalomyelitis, myelopathy associated with human T-cell leukaemia virus type-1, leukodystrophia, AIDS or paraneoplastic syndrome. Focal involvement of the CNS (vascular pathologies, spinal compression, cervical cord spondilogenetic myelopathies, Arnold-Chiari malformation, transverse myelitis, anterior medullar ischaemia, ischaemic optic neuropathy, Leber's hereditary optic neuropathy) can also mimic MS (Table 3).

Table 3: Differential diagnosis of MS[20]

Disease	Presentation/features, methods/measurements aiding diagnosis
Diseases clinically similar to MS, but with a differential diagnosis after magnetic resonance imaging	
Wegener granulomatosis	Presence of both granulomas and vasculitis lesions
Whipple's disease	Presence of an oculomasticatory myorhythmia
Arnold-Chiari malformation	Abnormality of the cranium–cervical region without lesions in the white matter of the brain
Compressive lesions on the spinal cord	Individuation of the lesion
Vitamin B12 deficiency	Symmetrical involvement of posterior and lateral columns
Intracranial tumours	Individuation of the lesion
Diseases clinically and radiologically similar to MS	
AIDS	Anti-HIV antibody in serum
Cerebral vascular diseases	Electrocardiogram; extracranial Doppler sonography; echocardiography; concentrations of protein C, protein S, antithrombin III and lupus anticoagulant; identification of factor V Leiden mutation
Spinocerebellar ataxia	Clinical course of the illness (progressive course without remissions); normal evoked potentials
Mitochondrial encephalopathy	Plasma and cerebrospinal fluid concentrations of lactate and pyruvate; analysis of mitochondrial DNA; muscle biopsy
Cerebral autosomal-dominant arteriopathy with subcortical infarcts and leucoencephalopathy (CADASIL)	Clinical course of the illness; genetic linkage analysis; angiopathic lesions
Diseases clinically, radiologically and with cerebrospinal fluid characteristics similar to MS	
Vasculitis	Antinuclear antibodies (ANA); antibodies against extractable nuclear antigens (ENA), SS-A, SS-B and double-stranded DNA; antineutrophil cytoplasmatic antibodies (c- and p-ANCA); antiphospholipid antibodies; cerebral angiography; retinal fluorangiography; biopsy
Neuro-Behcet's disease	Clinical course of the illness (ulcerations of the skin and mucosa)
Lyme disease	Antiborrelia antibodies in plasma and cerebrospinal fluid; positive result from Lue TPHA test for syphilis
Sarcoidosis	Kveim's test; concentration of angiotensin-converting enzyme in plasma and in cerebrospinal fluid; biopsy of a lesion
Adrenoleukodystrophy	Individuation of the long chain fatty acids
Human T-cell leukaemia virus type 1 (HTLV-1)	Individuation of anti HTLV-1 antibody
Leber congenital amaurosis	Analysis of mitochondrial DNA (position 11778)
Acute disseminated encephalomyelitis	Serial magnetic resonance imaging scans; clinical course of the illness

Variants of MS

Variants of MS also need to be distinguished from other inflammatory demyelinating diseases of the CNS. Such variants differ in the extent, degree and localization of tissue damage, as well as in their clinical features, course, prognosis and therapeutic strategies. The clinical/MRI aspects typical of neuromyelitis optica (also called Devic's disease), Marburg's disease, Schilder's sclerosis and Balo's sclerosis and the clinical/paraclinical tools used in differential diagnosis need discussing in more detail.

Lecture 5: Prognosis in Clinically Isolated Syndrome and MS

After diagnosis it is useful to identify the demographic and clinical factors and MRI measures that help clinicians determine a patient's prognosis. Students need to be aware of the demographic and clinical data associated with a less favourable outcome, such as age, gender, certain symptoms, progressive course at disease onset, degree of recovery from the first relapse, time to a second neurological episode, number of relapses in the first 5 years and time to an EDSS score of 4.[21] The effects of relapse on short- and long-term disability and the protective effect of pregnancy and possible recurrence after delivery should also be introduced.

Magnetic resonance imaging may be superior to clinical features in predicting clinical outcome as it allows detection of sub-clinical disease activity, especially in the early disease phase. This needs to be explained and details given of the established MRI parameters used to evaluate MS disease outcome, such as the number of Gadolinium-enhancing lesions,[22] lesion volume on T2-weighted images,[23] number and volume of T1 hypointensities or 'black holes' and brain atrophy. The prognostic value of MRI in the clinically isolated syndrome (CIS) and in RR forms of MS needs to be explained. This technique can be used to predict the development of MS,[24] the relapse rate and changes in disability progression over time.

Subtle pathological changes other than those defined by conventional MRI techniques may be present from the early phases of MS and become increasingly important contributors to clinical progression later in the disease course. Neurologists need to be aware of these changes and of new MRI scanning techniques being developed to detect them. Non-conventional MRI techniques, such as magnetic resonance spectroscopy, magnetization transfer imaging, diffusion-weighted imaging, diffusion-tensor imaging and functional MRI, identify abnormalities in the normal appearing white matter and cortical/subcortical grey matter. They also indicate the recovery potential following a reorganization of functions due to brain plasticity. Adaptive changes in the cerebral cortex during a motor task have been observed with functional MRI in patients with MS.[25] Recruitment of additional cortical areas of the sensory–motor network is confined to the contralateral hemisphere in patients with scattered white matter lesions and no previous symptoms of motor deficit, involving the ipsilateral sensory–motor network in patients with a previous hemiparesis and a larger number of lesions specifically located along the corticospinal tract (Figure 2). Extension of activation of motor areas may represent a compensatory mechanism that allows a normal motor function to be maintained despite selective damage to the corticospinal tract.

Recent studies on genetic markers suggest that they influence susceptibility to MS and also to its prognosis. A discussion of these markers, including polymorphisms in the interleukin-1 receptor antagonist[26] and immunoglobulin G-Fc receptor,[27] is warranted, therefore.

Lecture 6: Treatment of MS

Therapeutic options available

The fact that patients affected by MS need support in two ways should be emphasized. Non-pharmacological

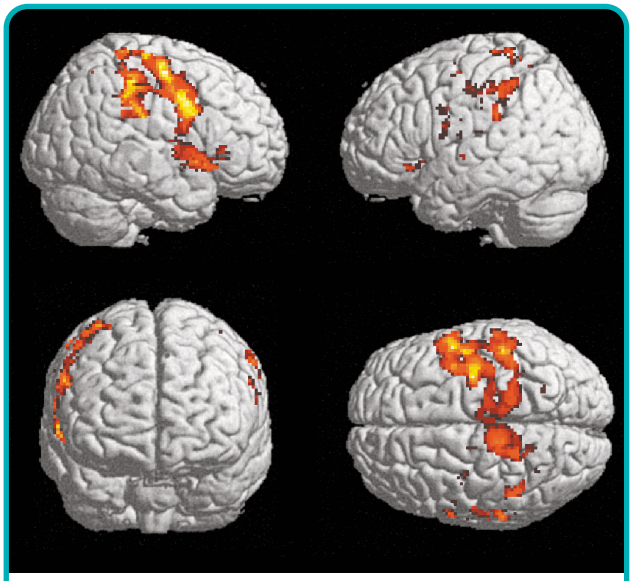

Figure 2. Results of between-group comparison by one-way ANOVA, showing significantly more activated cortical foci in the group of patients with a single clinical attack consisting of hemiparesis than in the groups with a single attack consisting of optic neuritis and controls, at a level of significance of uncorrected $P<0.001$ (courtesy of Dr Patrizia Pantano.)

therapies include physiotherapy and psychotherapy; the former maximizes strength in functional body parts, which helps accelerate recovery from relapse, and the latter provides support in coping with the different stages of disease and treating mood disturbances. Pharmacological therapies aim to reduce the frequency and severity of relapses and delay disability progression.

Treatment to modify the natural history of MS

Preventive therapies are available for use at different stages of the MS disease course (first episode, RR, SP). The rationale for using immunomodulators and immunosuppressants in MS should be presented and their different mechanisms of action examined. The following paragraphs briefly describe the main points to be discussed.

Research into disease-enhancing interferon gamma led to development of a favourable disease-modifying drug, interferon beta. Interferon beta-1a and -1b both have demonstrated safety, tolerability and efficacy when used to treat MS; clinical trial results show that they reduce the relapse rate and slow disability progression. Data obtained from clinical trials can be confirmed by analysing the effects achieved in daily clinical settings. It would be useful to focus on the CIS, making reference to studies noting a reduction in the rate of conversion to clinically definite MS as a consequence of early treatment with interferon beta. Interferon therapy is far more effective the earlier it is started, highlighting the need for early diagnosis and treatment initiation. The presence of inflammation-induced axonal damage, even in the early stages of the disease, provides an additional rationale for early treatment with inflammation-reducing drugs, since axonal transection is irreversible and is most abundant in areas of inflammation. Worldwide trials are ongoing to determine which patients respond best to interferon beta therapy, the optimal dose and time at which to initiate therapy and the efficacy of long-term therapy. The efficacy of interferon betas for treating SP forms of MS in the presence/absence of persisting inflammatory activity should also be discussed. Other therapies warranting discussion are glatiramer acetate,[28] immunosuppressants such as mitoxantrone,[29] and azathioprine, and natalizumab.[30] Natalizumab, an α4-integrin antagonist, has recently been licensed as it was shown to reduce the relapse rate and development of inflammatory brain lesions in Phase III placebo-controlled trials in patients with RRMS.* Some trials with this drug are ongoing so that 2-year data can be produced. For each drug, it is useful to discuss data on efficacy in the short- and long-term periods, the type of clinical course in which the treatment is most useful, any side-effects or adverse events, and the existence of a dose effect. The lack of effective treatment/limits of existing treatments for primary progressive MS should be noted.[31]

Research into the best way to use existing therapies and development of novel ones continues and should be studied. Combination therapies (i.e., interferon beta plus an oral immunosuppressant) may produce better results than monotherapy; development of neuroprotective therapies should become an MS research objective, given the neurodegenerative component of the disease. In addition, new therapeutic strategies are being researched such as: next-generation chemotherapeutics; new immunosuppressant agents; monoclonal antibodies; anti-leucointegrin humanized antibody; altered peptide ligands; T-cell receptor vaccines; adenosine deaminase inhibitors; sex hormones; statins; autologous bone marrow transplantation and staminal transplant cells.

Treatment of MS relapses and MS symptoms

Outline the treatment of relapses using high doses of corticosteroids. Pharmacological treatment of other symptoms associated with MS, such as spasticity, pain, bladder disturbances, bowel and sexual dysfunction, fatigue, depression and anxiety, also need to be covered.

Lecture 7: Management of MS

Models of caring

The 'social burden' of MS and financial costs of the disease need to be explored. In addition, the importance of a specialized centre devoted to treating and managing MS should be highlighted, and details of how to organize such a centre given. A multidisciplinary team is needed to achieve comprehensive management of the different aspects of MS at the different disease stages. Models of a 'hospital at home' and hospital care versus home-based management could be debated.[32]

Caregiver

The trainee neurologist needs to understand the effects of MS on the patient and their caregivers. The

*At the time of acceptance of this article, natalizumab was licensed; however, it availability has since been suspended due to safety concerns.

relationship between caregiver and patient is an important one, and interactions can occur between the emotional distress of the caregivers and the health status of the patient. Physicians need to learn the importance of managing the caregiver as a 'second patient' and to consider him/her as a legitimate target for medical intervention.[33]

Lecture 8: MS in Childhood

The clinical features, MRI characteristics and diagnostic aspects peculiar to MS in children as well as perspectives on treatment should be presented.[34,35]

Two MRI Reading Sessions with a Specialist Neuroradiologist

Before describing the radiological features typical of MS, it is useful to provide a brief description of the most useful MRI sequences. Proton density and T2-weighted images emphasize hyperintense lesions that represent different degrees of oedema, inflammation and demyelination, while the fluid-attenuated inversion recovery sequence (FLAIR) emphasizes particular sites where lesions are located. Post-contrast T1-weighted images reveal the hypointense lesions known as 'black holes' and indicate irreversible tissue loss. Finally, hyperintense lesions (contrast enhancing lesions) are due to disruption of the BBB. Once the technology has been introduced, guidelines on how to read and interpret MRI images can be provided. This should be extended to cover the new radiological techniques often used in research.

Practical Training in the Clinic

Practice in an MS clinic with patients at various stages of the diagnostic and therapeutic process is invaluable. During this time students need to become competent at performing a lumbar puncture. Students also need to familiarize themselves with available treatment options, providing patient support and the most promising lines of research likely to prevent or reduce disability brought about by MS.

Conclusions

Few studies have reported the value of different intervention methods on improving medical education in the field of neurology or on students' performance.[36–38] We believe, however, that the type of clinical activity used in medical learning affects educational success. In our opinion, a PBL course combined with intensive bedside teaching could be successfully integrated into a traditional curriculum and would enhance knowledge assimilation. This type of course maintains the important role that teachers play and enables them to help students to observe and reason. In addition to teaching the subject, lecturers and tutors would be developing their students' independent study methods and thought processes – skills that will be valuable throughout life.

New discoveries are publicized at scientific meetings and through specialist journals and educational events organized by societies like ECTRIMS, ACTRIMS and the Charcot Foundation. We hope that guidelines on education can be disseminated in these ways, but also through meetings attended by a large audience of general neurologists, such as those organized by the European Federation of National Neurological Societies (EFNS). These meetings attract members from national societies in more than 35 countries, and EFNS publications reach an even wider audience. Dissemination in this way would be more effective than holding meetings dedicated to education and MS. The *MS Forum* monographs provide continuous education on scientific and therapeutic progress in MS; they describe the organization of healthcare delivery and MS services, and inform about health economics. The monographs also guide students on how to communicate effectively with patients, and where patients and their families can find support.[39]

More than with other neurological diseases, the young patient affected by MS – who is suddenly faced with a difficult and still uncertain future – is a person, not just a patient. Her/his expectations in life should be encouraged, continuous support provided through all clinical events, and the hope generated by new research advances passed on and explained; all of this requires not just a specialist, but a 'special neurologist'. We need to get the training right at all levels to produce such neurologists.

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Conflicts of Interest

No conflicts of interest were declared in relation to this article.

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