UPDATE OF MULTIPLE SCLEROSIS PART II

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Summary
Introduction: Multiple sclerosis (MS) is an autoimmune demyelinating disease of the central nervous system, the aetiology of which remains so far unknown and which probably involves genetic, immune, inflammatory, as well as environmental factors. OBJECTIVES: A review of the current and past literature on multiple sclerosis to provide a concise and comprehensive educational resource mainly for postgraduate medical students, but also for undergraduate medical college students as well as other medical practitioners and their patients. The aim being to present a simplified and clinically relevant summary of the main manifestations, and management of multiple sclerosis, with an update on current theories of pathophysiology, aetiology; and the basis behind the therapeutic agents used in current clinical practice. METHODS: The standard medical texts and journals relating to MS were consulted as well as reliance on own experience of patients attending the teaching hospitals, and clinics in Benghazi Libya with a diagnosis of multiple sclerosis. Local and worldwide epidemiological published data were also reviewed. RESULTS: The incidence of multiple sclerosis varies worldwide. Eastern Libya is an area of high risk MS incidence. The importance is emerging of a genetic role in the already known immune pathogenesis of multiple sclerosis. Diet and light have regained importance in the aetiology of the disease. Investigations are advancing and help to differentiate the disease from other mimicking conditions. Biomarkers help to define diagnosis and determine prognosis. CONCLUSIONS: Multiple sclerosis is an important neurological disease with protean CNS manifestations which must be considered in the differential diagnosis of neurological symptoms at all ages; although commonly considered a disease of young people, especially females. A countrywide database may help to collate efforts and resources, as well as unify data regarding the number and presentation of patients, to assess their requirements.

Keywords: multiple sclerosis - pathophysiology - clinical presentation - management

Received: September 19 2017
Accepted: December 03 2017

TREATMENT OF MULTIPLE SCLEROSIS (1-8, 27, 33, 39-56) Can be divided into general: symptomatic, and supportive; and specific, aimed to modify the disease and lessen relapse rates. We still do not have a final curative treatment, but most patients can live a healthy and active life. Management is done best with a multidisciplinary team approach. Precautions must be taken to lessen exposure to infection. The patient must be supported psychologically. Although it is sometimes recommended to avoid the hepatitis B vaccine, in areas of high risk, the benefit of the vaccine probably outweighs the risk, and there are no firm data that the vaccine affects the risk of multiple sclerosis. Pregnancy does not worsen the long-term prognosis in patients who are well supported. General supportive and symptomatic management remains the cornerstone of multiple sclerosis management, especially when / where disease modifying therapy is not possible. (3, 4, 27) PHARMACOLOGICAL TREATMENT OF ACUTE RELAPSES AND PROPHYLACTIC THERAPIES INCLUDING NEW THERAPIES: (1-8, 14, 18, 19, 27, 29, 33, 38--56). In relapsing-remitting multiple sclerosis intravenous methylprednisolone (IVMP) is the treatment of choice to shorten the relapse duration. There is some evidence that repeated use may also limit progression. (1-8, 14, 27, 29, 56) In optic neuritis contradictory data exist, probably it supports giving IVMP. (40, 41) Leber’s hereditary optic neuropathy should be excluded (3, 4) before giving IVMP. Other therapies for resistant relapses are plasma exchange, and IV human immunoglobulin. (4, 56) Immune-modulating therapies (disease modifying agents): aim to prevent further relapses, and limit progression: Interferon beta 1a or 1b injections. The commercial formulations of interferon beta are subcutaneous (S/C) Rebi,©

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Betaferon®, Betaseron® intramuscular [IM] Avonex®. Rebi® is available in two strengths. The alternative agent in current usage for some patients with MS is Glatiramer acetate (Copaxone®) S/C. Beta interferons may work in several ways, perhaps mainly by turning the balance in favour of helpful interleukins, and lessening the effect of harmful ones. Glatiramer acetate may work by blocking harmful immune pathways. Antibodies to these therapies are known to occur with continued use, and biomarkers are useful in deciding along with clinical parameters who would benefit from therapy, and when to change from one agent to another. (3, 4, 27, 33, 39, 46, 48-55) Others therapies that have been tried in patients with multiple sclerosis with varying success include: monthly IV human immunoglobulin, (56) azathioprine +/- oral prednisolone, acyclovir, and angiotensin converting enzyme inhibitors. (4, 33) Pulsed oral methylprednisolone 500 mg for three days per month with interferon beta 1a has recently been found useful. (50) New emerging therapies showing promise include: IV alemtuzumab / Campath®, (a monoclonal antibody therapy), (66) and oral therapies and / or patchs, e.g. beta interferon/oral and patch) and laquinimod (oral). (4, 45, 46) Growing evidence supports a potential role of vitamin D supplementation in preventing MS, and now as an important adjuvant therapy in treating established MS. (4, 63) Over the years many neurologists have treated patients with vitamin B12 supplements and report favourable clinically observed long-term effects. (1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 27, 67, 68, 69)

DURATION OF THERAPY WITH BETA INTERFERON AND GLATIRAMER ACETATE: The above criteria are based on Association of British Neurologists Guidelines for the use of Beta Interferons and Glatiramer Acetate in Multiple Sclerosis, January 2001. (53) Actually for most teams worldwide including Britain and Libya, the treatment criteria are taken as each new case on its own merits, and have become less rigid despite the financial cost involved. Most patients are offered some form of disease modifying agent. For both interferon beta and glatiramer acetate, a formal review is made at two years, if patient and neurologist agree that there is a beneficial effect, it should be continued indefinitely. Although some patients with good prognostic indicators may not require to be on long-term therapy, there is no current firm evidence base of the exact duration required to achieve cure. (4, 8, 27, 33, 38, 53)

PHARMACOLOGICAL TREATMENT OF SECONDARY PROGRESSION: (2, 3, 4, 8, 18, 19, 27, 38, 45, 46, 50, 52, 54, 55) Beta interferon and copaxone have shown minimal effects on secondary progression including atrophy and are usually continued for secondary progression. (4, 55) The following therapies are also used with variable success: oral azothioprine (exclude thiopurine S-methyltransferase deficiency, an autosomal recessive trait causing excessive thioguanine nucleotide accumulation in haematopoietic tissues which can result in severe and possibly fatal myelosuppression and liver dysfunction), cyclophosphamide, cyclosporine, methotrexate, mitoxantrone (cardiotoxic), or monoclonal antibodies: e.g. natalixumab (Tysabri®), rituximab a B cell specific monoclonal antibody. All are toxic agents with severe side-effects and cases are selected and monitored cautiously. IV Alemtuzumab has been used with some success, (66) made recently IV ocrelizumab. (71) Cladribine is an adenosine deaminase -resistant nucleoside analog that ablates subpopulations of lymphocytes. As an active triphosphate analog, cladribine triphosphate becomes incorporated into DNA of dividing cells, leading to DNA damage and subsequent cell death. Currently, cladribine is an approved treatment for hairy cell leukaemia and lymphoma. It may be useful in both primary progressive disease (PRMS) and relapsing-remitting disease (RRMS). (4) Patients are selected for treatment with caution for all the second line therapies. (2, 3, 8, 18, 27, 38, 45, 46, 50, 52, 54, 55) In all the above, papova virus infection must be excluded before commencing immunosuppressive agents. (33) It is best to select out patients early for these therapies.

PHARMACOLOGICAL TREATMENT OF PRIMARY PROGRESSIVE MULTIPLE SCLEROSIS: Primary progressive disease, until recently had no confirmed effective therapy, a few respond to rituximab, or cladribine. (1, 2, 3, 4, 8, 27, 66) IV ocrelizumab has been recently discovered to be effective in both primary progressive and relapsing remitting multiple sclerosis. It is currently the only available effective therapy for the primary progressive type. (71)

ATROPHY, DISABILITY AND REHABILITATION ISSUES: Although traditionally a white matter disease, brain and spinal cord atrophy on MR imaging, are now well recognised as clinical imaging
manifestations of progressive disease. (4, 8, 19, 25, 26, 27) They reflect axonal damage and grey matter involvement. Sometimes the atrophy may be quite marked with marked paradoxical ventricular enlargement leading to diagnostic controversy. Early development of atrophy is a prognostic indicator and may be a therapeutic challenge. (75) Clinical scales are in use to measure the neurological mobility dysfunction, and have proved helpful in monitoring patients on disease modifying therapies, and in research trials. These scales are also used by social services to decide patients' requirements, and arrange necessary social support for the patient, and family. Table-7 demonstrates the Kurtzke extended disability scale. (59) Other measurements for cognitive function and bladder function (e.g. urodynamic studies) are necessary to complete the clinical assessment. Most patients benefit from exercise, (47) a healthy life routine, as well as programmes of rehabilitation, and physiotherapy tailored to their individual requirements.

RESEARCH:
New therapies might:
1) Work on sodium channels. There is some evidence that such drugs e.g. carbamazepine might have regenerative qualities, but the side-effects of recurrence or worsening on stopping the agents has not been finally evaluated. (61, 62) Amitriptyline which has both noradrenergic and sodium channel blocking effects may be equally beneficial but again has not been evaluated at the cellular and clinical levels.
2) Enhance mitochondrial function e.g. coenzyme Q10 (ubiquinone). (65)
3) Work in new novel mechanisms that promote nerve function e.g. levetiracetam. (64)
4) Modulate genetic function by promoting protective mechanisms.
5) Promote protective environmental mechanism: Further research into the effect of dietary agents. (63, 67, 68, 69)
6) Involve stem cell therapy.
7) Finally new options may even be purely surgical! A small, open-label study suggested that internal jugular vein and azygous vein angioplasty had a positive effect on some MS symptoms. (4)

CONCLUSIONS:
Multiple sclerosis is an important and challenging neurological disease with protean central nervous system (CNS) manifestations. Although commonly considered a disease of young people especially females, it must be considered in the differential diagnosis in both genders at all ages. A countrywide database may help to collate efforts and resources, as well as gain more information regarding the number and presentation of patients, not only to assess their health service requirements but, also to further research into the aetiology and treatment of the disease. Advances in both cerebrospinal fluid analysis, (33) and MRI (25, 26, 70) in particular, have simplified the diagnostic and prognostic process, and are a field of continuing research and development. The final answer regarding multiple sclerosis is awaited.

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Indications

- Keratoconus,
- Pelucid marginal corneal degeneration (PMCD),
- Post-LASIK ectasia,
- Post CXL (Corneal collagen cross-linking),
- Post corneal graft or penetrating keratoplasty
- Post INTACS/ICRS (Intrastromal corneal ring surface)