Welcome to this special issue of Neurology Research Review, focusing specifically on multiple sclerosis (MS).

Our understanding of MS, like many areas of neurology, has undergone a revolution driven by neuroimaging and molecular biology. In this review we discuss new thinking on the diagnosis of MS based on MRI findings, and discuss subtypes of neuroinflammation that we are separating off from MS, particularly neuromyelitis optica (NMO). We will also try to bring some clarity to a wave of exciting, complex and expensive treatments that have appeared for MS that will transform the way we think about and manage the condition.

Wallace Brownlee has co-edited this review. Wallace has just finished his NZ training as a neurologist and is about to depart for the UK to take up a fellowship in neuroinflammatory disorders. He is part of a new wave of young neurologists taking an active interest in the management of MS and related disorders.

We hope you find this special issue interesting and look forward to hearing your comments.

Kind regards,
Dr Barry Snow
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Diagnostic criteria for multiple sclerosis: 2010 revisions to the McDonald criteria

Authors: Polman C et al

Summary: Since the revision of the McDonald diagnostic criteria in 2005, there has emerged a need to simplify them to improve their comprehension and utility. As a result, the International Panel on Diagnosis of MS met in Ireland in May 2010 to further revise the McDonald criteria. The 2010 revisions will in some instances allow a more rapid diagnosis of MS, with equivalent or improved specificity and/or sensitivity compared with past criteria and will in many instances clarify and simplify the diagnostic process with fewer MRI examinations. The revisions also address the applicability of the criteria across populations, and may allow earlier diagnosis and more uniform and widespread use.

Comment: We make a clinical diagnosis of relapsing-remitting MS when the patient has had two episodes of neurological dysfunction separated in both time and space. At the first clinical attack most patients have MRI evidence of asymptomatic demyelination. Rather than waiting for a second clinical episode, the McDonald criteria described in this paper incorporates MRI to allow us to make a diagnosis of MS. We need to see lesions in a typical distribution for demyelination particularly in the white matter of the brain and spinal cord. While MRI has revolutionised the diagnosis of MS, the critical point is that the episodes must be clinically consistent with demyelination. Patients still need a careful neurological assessment before we can make a diagnosis. Clinical medicine is not dead!


CSF abnormalities can be predicted by VEP and MRI pathology in the examination of optic neuritis

Authors: Horwitz H et al

Summary: This study retrospectively evaluated whether CSF abnormalities can be predicted by MRI and visual evoked potential (VEP) pathology in patients with suspected optic neuritis. 437 patients referred by ophthalmologists to an optic neuritis clinic were included; none of the patients had MS prior to their referral. All of the patients underwent MRI, a lumbar puncture and VEP. CSF leukocytes and the IgG index were elevated in 33% and 41% of patients, respectively, and oligoclonal bands were detected in 61% of patients. CSF abnormalities were strongly correlated with VEP and MRI (p<0.0001). Patients with normal VEP and MRI were likely to have a normal lumbar puncture. In conclusion, patients with suspected MS should be evaluated with VEP and MRI before considering a lumbar puncture.

Comment: Historically, a lumbar puncture looking for oligoclonal bands and evoked potentials looking for evidence of asymptomatic demyelination in the visual, auditory and somatosensory pathways were important paraclinical investigations to help make a diagnosis of MS. With MRI the role of these investigations has diminished. Lumbar punctures are feared by patients and are associated with morbidity in the form of post-lumbar puncture headache. We reserve lumbar punctures for situations where there is some unusual aspect to the clinical picture or imaging findings.

Reference: J Neural 2012;259(12):2616-2620
http://link.springer.com/article/10.1007/s00415-012-6551-1
Does interferon beta treatment exacerbate neuromyelitis optica spectrum disorder?

Authors: Kim S-H et al

Summary: Patients with neuromyelitis optica (NMO) experience clinical deterioration when treated with interferon beta (IFN-β). This study retrospectively evaluated the extent to which IFN-β exacerbates NMO spectrum disorders (NMOSD). Medical records of 40 patients with NMOSD who had been treated with IFN-β for >6 months and whose disease duration was >1 year at the start of IFN-β treatment were reviewed. Annualised relapse rates (ARR) and Expanded Disability Status Scale (EDSS) scores before and after IFN-β treatment were evaluated. 95% of patients had an ineffective or exacerbated response to IFN-β treatment. The mean ARR significantly increased after treatment with IFN-β (p=0.002), as did the mean EDSS score (p<0.001). In conclusion, IFN-β is ineffective for preventing relapses and may even increase relapses in patients with NMOSD.

Comment: What we know as MS is likely to be a collection of disorders. One that has emerged as distinct is NMO. This is an often vicious demyelination of the optic nerves and spinal cord. Patients can present with sequential bilateral visual loss or devastating spinal cord lesions. While MS is more common in Caucasians, NMO often occurs in people from the Pacific Rim. Many patients have specific antibodies to the aquaporin4 water channel, which is concentrated in the optic nerves, brainstem and spinal cord. We test for this antibody as part of the diagnostic workup. Standard interferon treatment for MS appears to make NMO worse. Instead, we use immune suppression with agents that don’t work so well for MS such as azathioprine or mycophenylate. It is likely that we will discover more specific antibodies that separate out other subtypes of demyelinating disorders from what we now consider standard MS.

http://dx.doi.org/10.1177/1352458512439439

Early predictors of non-response to interferon in multiple sclerosis

Authors: Horakova D et al

Summary: This study determined early clinical and MRI predictors of non-response to interferon (IFN) treatment in patients with MS. 172 patients with relapsing-remitting MS treated with IFN-β were assessed during the initial year of treatment for disability and its progression, relapse score, brain volume change, brain parenchymal fraction, number of new T2 lesions, and T2 and T1 lesion volume. Treatment non-response was evaluated as confirmed disability progression or overall annual average relapse score >1 over the following 5 years. 90 patients (52%) reached the status of IFN non-responders in years 2–6. The risk of future treatment non-response was significantly increased in patients with ≥1 new T2 lesions and a relapse score ≥2 (odds ratio = 2.7) or those with ≥3 new T2 lesions regardless of the relapse score (odds ratio = 3). In conclusion, in patients with MS treated with IFN-β for 1 year, the number of new T2 lesions and the annualised relapse score predict risk of non-response to IFN-β over the following 5 years.

Comment: The first-line disease modifying treatments for MS have now been in use for 20 years. While generally well tolerated the effects are modest with a one-third reduction in relapse rate and probably only a minor impact on long term disability. Many patients do well on these treatments, but a substantial number don’t. It is important to identify the poorly responding group, particularly as more effective treatments are now available. In this study the development of new MRI lesions while on treatment with beta interferon predicted a worse outcome, even among patients who were free of clinical relapses.

http://dx.doi.org/10.1111/j.1600-0404.2012.01662.x

Effects of interferon beta-1b on cognitive performance in patients with a first event suggestive of multiple sclerosis

Authors: Penner I-K et al

Summary: This study analysed data from the BENEFIT study to evaluate the impact of IFNβ-1b on cognitive performance in patients with early-stage MS. In the BENEFIT study, 468 patients with MS in the clinically isolated stage (CIS) were randomised to receive either IFNβ-1b 250µg subcutaneously every second day or placebo for two years or until a diagnosis of clinically definite MS (CDMS). After conversion to CDMS or after 2 years, patients were offered open-label IFNβ-1b for up to 5 years. The current analysis evaluated cognitive performance (assessed by Paced Auditory Serial Addition Test-3”; PASAT-3” score) during the placebo-controlled and follow-up phases of BENEFIT. Improvement in PASAT-3” score from baseline was greater in IFNβ-1b than placebo recipients in patients not reaching CDMS by year 2. The treatment effect was maintained at year 5. In conclusion, early IFNβ-1b treatment had a sustained positive effect on cognitive performance in patients with early-stage MS.

Comment: Cognitive impairment is common and often disabling in early MS. Half of people with MS stop work in the first four years of their disease, and this is often driven by problems with concentration, memory and fatigue rather than physical disability. It is also under-recognised by clinicians and researchers; the end points of clinical trials are heavily weighted for physical measures. In this study, early treatment with disease modifying treatment maintained cognition for five years of follow up. This is consistent with a general trend for earlier treatment for all aspects of MS.

http://msj.sagepub.com/content/18/10/1466.full

Risk of natalizumab-associated progressive multifocal leukoencephalopathy

Authors: Bloomgren G et al

Summary: This study determined the risk of progressive multifocal leukoencephalopathy (PML) associated with natalizumab treatment in patients with MS. Data from postmarketing sources, clinical studies and an independent Swedish registry were analysed to estimate the incidence of PML in MS patients taking natalizumab. PML risk was quantified according to presence or absence of anti-JC virus antibodies, prior or no prior use of immunosuppressants, and duration of treatment. 212 cases of PML were found among 99,571 natalizumab recipients (2.1 cases per 1000 patients). Patients who were positive for anti-JC virus antibodies, had taken immunosuppressants before starting natalizumab, and had received 25–48 months of treatment with natalizumab had the highest estimated risk of PML (11.1 cases per 1000 patients). The risk of PML was lowest in patients who were negative for anti-JC virus antibodies (0.09 cases or less per 1000 patients).

Comment: Natalizumab is the most effective treatment we have for MS that is not controlled by standard disease modifying agents. Access to natalizumab is restricted by funding, and about 20 New Zealanders are currently being treated. All immune suppression carries the risk of opportunistic infection. In the case of natalizumab, the feared infection is PML, a brain infection due to reactivation of the JC virus. We are familiar with PML in HIV infection and transplant patients on immune suppression. This paper helps us determine the risk of PML in individual patients who are candidates for treatment with natalizumab.

http://dx.doi.org/10.1056/NEJMoa1107829

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Placebo-controlled phase 3 study of oral BG-12 for relapsing multiple sclerosis
Authors: Gold R et al for the DEFINE Study Investigators
Summary: This study evaluated the efficacy of BG-12 (dimethyl fumarate) in patients with relapsing–remitting MS. Patients were randomised to receive oral BG-12 240mg twice daily, 240mg three times daily, or placebo. The estimated proportion of patients who had a relapse within 2 years was 27% in those taking BG-12 twice daily, 26% in those taking BG-12 three times daily, and 46% in those taking placebo (p<0.001 for both BG-12 regimens vs placebo). The annualised relapse rates at 2 years were 0.17, 0.19 and 0.36 in the respective groups, representing relative reductions of 53% and 48% with the respective BG-12 regimens (both p<0.001 vs placebo). Adverse events associated with BG-12 included flushing, gastrointestinal events, decreased lymphocyte counts and elevated liver aminotransferase levels. In conclusion, both BG-12 regimens reduced the proportion of patients who had a relapse, the annualised relapse rate, the rate of disability progression, and the number of lesions on MRI.

Comment: The conventional disease modifying treatments for MS are all injectable. Injectable treatments are unpopular with patients, and they often don’t take them. Oral disease modifying treatments are now available and in development. The most exciting of these is BG-12 (dimethyl fumarate), which has been used in Germany for psoriasis for 20 years. The results in MS are impressive with a significant reduction in clinical and radiologic disease activity. The side effect profile is favourable with flushing and elevated liver enzymes which tend to improve with time. Importantly no long term safety concerns have emerged.

http://dx.doi.org/10.1056/NEJMoa1201427

Interferon beta for secondary progressive multiple sclerosis
Authors: La Mantia L et al
Summary: This Cochrane review examined the effects of interferon on disability progression in patients with Secondary Progressive Multiple Sclerosis (SPMS). Data from 5 randomised, double or single blind, placebo-controlled trials that evaluated the efficacy of interferons versus placebo in 3122 patients with SPMS were included in the analysis. The population was heterogeneous in terms of baseline clinical disease characteristics. IFN-β 1a and 1b did not decrease the risk of progression sustained at 6 months after 3 years of treatment. Significant decreases were seen in the risk of progression sustained at 3 months and the risk of developing new relapses at 3 years. Data obtained from single MRI studies showed that the risk of developing new active brain lesions decreased over time. In conclusion, interferons do not prevent the development of permanent physical disability in patients with SPMS.

Comment: In early MS most patients have a relapsing-remitting disease course with periods of months or years without new symptoms. After 10–15 years of relapsing disease about half of patients develop secondary progressive MS with insidious neurologic deterioration often without clear cut relapses. The conventional disease modifying treatments including beta interferon do not seem to slow the accumulation of disability in patients with progressive MS. This is an important patient group and there is an urgent need for effective treatments.

Reference: Cochrane Database of Systematic Reviews 2012;1CD005181
http://dx.doi.org/10.1002/14651858.CD005181.pub3

Sustained-release oral fampridine in multiple sclerosis: a randomised, double-blind, controlled trial
Authors: Goodman A et al for the Fampridine MS-F203 Investigators
Summary: This phase 3 study assessed the efficacy and safety of oral sustained-release fampridine in patients with ambulatory deficits due to MS. 301 patients were randomised to receive fampridine 10mg twice daily or placebo for 14 weeks in a double-blind design. Response was defined as consistent improvement on timed 25-foot walk; the primary outcome was the proportion of timed walk responders in each treatment group. 78 out of 224 (35%) fampridine recipients and 6 out of 72 (8%) placebo recipients were timed walk responders (p=0.0001). Walking speed improved by 25.2% in fampridine-treated timed walk responders compared with 4.7% in placebo recipients. Timed walk responders showed greater improvement in 12-item MS walking scale scores than timed walk non-responders (p=0.0002). In conclusion, fampridine improved walking ability in some people with MS.

Comment: Progressive MS most often takes the form of a slowly progressive spastic paraparesis leading to loss of ambulation. Patients with progressive MS rate mobility impairment as the main factor contributing to poor quality of life. The focus of treatment is rehabilitation and symptom management. Fampridine is a new formulation of an old medicine that blocks potassium channels to improve conductance in demyelinated axons. The net effect is a 25% improvement in walking speed in about a third of all patients. The major problem with this treatment is cost. Patients can get the first month of treatment free with the subsequent cost being $800/month. Some of our patients have had meaningful improvement, but the key message is that individual results vary and only continue treatment if it makes a real difference.

Reference: Lancet 2009;373(9665):732-8
http://dx.doi.org/10.1016/S0140-6736(09)60442-6
Abridged Data Sheet

AVONEX® (Interferon beta-1a 30-microgram injection: Pre-Filled Syringe (PFS), BIO-SET® powder, and AVONEX PEN®).

**INDICATIONS:**
Treatment of relapsing forms of multiple sclerosis (MS). Treatment of patients who have experienced a single demyelinating event and are at risk of developing clinically definite MS based on MRI abnormalities characteristic of MS. **CONTRAINDICATIONS:** History of hypersensitivity to natural or recombinant interferon beta, albumin (BIO-SET powder only) or any other component. Current severe depression and/or suicidal ideation. Women who are, or plan to become, pregnant while on therapy. **PRECAUTIONS:** IM injection only. Use with caution in patients with depression and mood disorders, pre-existing seizure disorders (particularly if epilepsy is not adequately controlled with antiepileptics), severe renal failure, severe myelosuppression, cardiac disease, active liver disease or history of significant liver disease. In addition to normal monitoring tests for MS, complete and differential white blood cell counts, platelet counts and blood chemistry, including liver function tests, are recommended during AVONEX therapy. Liver function should also be tested prior to initiation of treatment. Patients with myelosuppression may require more intensive monitoring of blood cell counts. Reconsider treatment if patient becomes pregnant, develops seizures, depression or suicide ideation, or if hepatic transaminase levels increase significantly or are associated with clinical symptoms such as jaundice. Pregnancy Category D. Aflatoxic potential. Women of childbearing potential should take appropriate contraceptive measures during treatment. Lactation: Because of the potential for serious adverse reactions in nursing infants, a decision should be made whether to discontinue breast-feeding or therapy. **INTERACTIONS:** Use with caution and monitor appropriately if given with myelosuppressive agents or hepatotoxic drugs. Exercise caution in combination with medicinal products that have a narrow therapeutic index and are largely dependent on the hepatic cytochrome P-450 system for clearance, e.g. antiepileptics and some classes of antidepressants. Corticosteroid or ACTH treatment can be used concomitantly. **ADVERSE EFFECTS:** Common: Flu-like symptoms (usually diminish with continued treatment), headache, muscle stiffness, pain or spasm, asthenia, fatigue, nausea, anorexia, vomiting, diarrhoea, anaemia, depression, insomnia, hypoesthesia, rash, increased sweating, injection site pain, inflammation or bruising, development of neutralising antibodies (2-5%). Rare: Serious hepatic injury including hepatitis, autoimmune disorders. Very rare: Hepatic failure, pancreatitis, profound thrombocytopenia, congestive heart failure, psychosis. Frequency unknown: Allergic reaction, emotional lability, suicide ideation, seizures. **DOSAGE AND ADMINISTRATION:** Refer to package insert and observe usual precautions for IM injections. Dose: 30 mcg IM once weekly. An antipyretic analgesic may be given prior to the injection and for the next 24 hours to modulate the possible flu-like symptoms. Remove PFS or PEN from fridge half-an-hour before injection. Reconstitute BIO-SET powder gently — do not shake. Use in one patient on one occasion only. Contains no antimicrobial preservative. **MEDICINES CLASSIFICATION:** Prescription Medicine. **REFERENCES:**