Multiple Sclerosis Research Review™

Making Education Easy

Issue 4 – 2015

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Abbreviations used in this review:

BVL = brain volume loss;
CNS ADS = acquired central nervous system demyelinating syndromes;
CSA = cross sectional area; **DMTs** = disease modifying treatments;
DTI = diffusion-tensor imaging; **HBV** = hepatitis B vaccination;
HPV = human papillomavirus vaccination; **HSCT** = haematopoietic stem cell transplantation;
MRI = magnetic resonance imaging; **MS** = multiple sclerosis;
NEDA = no-evidence-of-disease-activity; **NPV** = negative predictive value;
NSBMS = Neuropsychological Screening Battery for MS;
OCT = ocular computer tomography; **PML** = progressive multifocal leukoencephalopathy;
PPV = positive predictive value; **RNFL** = retinal nerve fibre layer;
SDMT = Symbol Digit Modalities Test.

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Welcome to issue 4 of Multiple Sclerosis Research Review.

We lead this issue with a review article that provides an update on MRI techniques in MS and emerging techniques aimed to complement the current understanding of MS disease pathophysiology and which may facilitate the identification of markers to predict clinical outcomes.

A paper assessing the long-term safety and efficacy of alemtuzumab is included in this issue. Alemtuzumab is a new treatment for relapsing-remitting MS approved and listed on PBS from 1st of April 2015. The authors concluded alemtuzumab was associated with disease stabilisation in the majority of patients with highly active relapsing remitting MS over an average seven-year follow-up. However, there were a considerable amount of significant side effects; 48% developed other autoimmunity, predominantly thyroid disease.

A post hoc analyses of the phase 3 trials of fingolimod (FREEDOMS, FREEDOMS II, and TRANSFORMS) concluded the rate of brain volume loss in patients during the trials correlated with disease severity at baseline and new disease activity on study, and was associated with worsening disability. Analysis of a cohort from MSBase suggests in active MS during treatment with injectable disease-modifying therapies, switching to natalizumab is more effective than switching to fingolimod in reducing relapse rate and short-term disability burden.

The concluding article investigated autologous haematopoietic cell transplantation for MS. Although it is an effective treatment, multicentre controlled trials need to be conducted before a treatment with such high morbidity and mortality risk is offered to patients, even those with active disease.

We hope that you find the selection of papers helpful in your everyday practice, and we encourage you to send us your questions, feedback, and suggestions.

Kind Regards,

Associate Professor Jeannette Lechner-Scott
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MRI measures of neurodegeneration in multiple sclerosis: implications for disability, disease monitoring, and treatment

Author: Filippi M

Summary: The author reviewed the literature from a PubMed search of publications discussing magnetic resonance imaging (MRI) in Multiple Sclerosis (MS) from 2010 to 2013. The paper provides an update on the advanced MRI techniques in MS. Emerging techniques are also discussed that aim to complement the current understanding of MS disease pathophysiology and which may facilitate the identification of markers to predict clinical outcomes.

Comment: In the last two decades MRI has become the most relied upon diagnostic tool for MS. Not only is it used nowadays for diagnostic purposes but also to monitor disease activity. With the introduction of new techniques and steady improvement of scanner quality we notice how many lesions we have missed in the past years. In this review Fillippi summarises the large amount of recently published literature to which he has contributed substantially. He describes how new techniques like volumetric measurements of 3D sequences, not only of the whole brain but also grey and white differentiation, can monitor neurodegeneration over time. Techniques like diffusion trensor imaging, magnetisation transfer ratio or proton magnetic resonance spectroscopy can help detect early damage in normal appearing white matter and predict progression of disease. These techniques correlate far better with locomotor disability and cognitive decline than the previously relied upon T2 lesion load. They will help clinicians in future to tailor therapy to the individual and treat patients that are predicted to progress more aggressively at an earlier stage.

Reference: J Neurol. 2015 Jan;262(1):1-6

Abstract

Switch to natalizumab versus fingolimod in active relapsing-remitting multiple sclerosis

Authors: Kalincik T et al

Summary: This group used MSBase to identify patients with relapsing-remitting MS experiencing relapses or disability progression within the 6 months immediately preceding switch to either natalizumab (n=407) or fingolimod (n=171). The group reported the annualised relapse rates decreased from 1.5 to 0.2 on natalizumab and from 1.3 to 0.4 on fingolimod. They also found the change in overall disability burden differed between natalizumab and fingolimod (-0.12 vs 0.04 per year, respectively, p<0.001) quantified as area under the disability-time curve.

Comment: MSBase collects data prospectively from over 35,000 patients worldwide with MS. All participating neurologists undergo EDSS training and enter at least yearly EDSS scores, relapses and MRI data in an online database. This vast amount of data gives unlimited opportunities to conduct clinical relevant studies. With a statistical model called propensity matching, a virtual clinical trial can be conducted where out of the total number of patients entered two subgroups are selected that match in all major clinical criteria like age, sex, disease duration, EDSS and relapses in the previous 6-12 months etc. In this study they compared patients previously on injectable therapy that were switched to natalizumab or fingolimod. There was a clear difference in favour for natalizumab with regards to relapses and proportion of patients improving. Also, the area under the curve for annual EDSS was significantly less for natalizumab treated patients compared to fingolimod, although the classical measurement of sustained EDSS progression was not significant. Although this study cannot replace a formal head to head trial, in absence of such a study this can guide clinical decision making. Also, this study raises the issue, if the standard measurement of confirmed EDSS progression is actually too insensitive to detect change especially in trials for progressive disease.

Reference: Ann Neurol 2015 Mar;77(3):425-35
Abstract

Alemtuzumab treatment of multiple sclerosis: long-term safety and efficacy

Authors: Tuohy O et al

Summary: Alemtuzumab is the newest of treatments for relapsing remitting MS approved and listed on PBS from 1st of April 2015. This study reports the 7 year follow up data of the initial Cambridge cohort of 87 patients. All initial patients remained in the study. Depending which outcome measure is used (sustained EDSS progression or area under the curve) 68% or 60% have remained stable or improved. Again suggesting that the area under the curve is a more accurate reflection of clinical outcome. This needs to be compared to the natalizumab follow up data from TOP over 4 years, where 85% remained stable or improved. This does not reflect the now accepted no-evidence-of-disease-activity (NEDA) standard as MRI was not included in the analysis. They reported a considerable amount of significant side effects. 48% developed other autoimmunity, predominantly thyroid disease. One case of idiopathic thrombocytopenic purpura did not recover despite ongoing pulse steroid treatment. 13% had reactivation of varicella infections.

Comment: Although there is some suggestion that outcome is better when this treatment is given early, the potential risks associated with this treatment are speaking against using it as first line treatment. On the other hand limiting it to patients after natalizumab treatment has the risk that latent progressive multifocal leukoencephalopathy (PML) might end in a lethal outcome.

Reference: J Neurol Neurosurg Psychiatry 2015 Feb;86(2):208-15
Abstract

Evaluation of no evidence of disease activity in a 7-year longitudinal multiple sclerosis cohort

Authors: Rotstein DL

Summary: This study looked at yearly NEDA over 7 years in 219 relapsing remitting patients predominantly on injectable therapy. 46% were considered to have NEDA at 1 year and only 7.9% at 7 years. They found a positive predictive value (PPV) of NEDA at 1 year of 72% and at 2 years of 78%, whereas the negative predictive value (NPV) was 41% at 1 year and 43% at 2 years indicating that a prolonged period of stability is no guarantee for a good prognosis. Interestingly 7-11% were lost annually if MRI activity of the spine was included, which is not routinely done in clinical trials.

Comment: With more and more treatments available for relapsing remitting MS our goal for treatment response is constantly shifting. The introduction of beta-interferon achieved relapse reduction, the natalizumab trials measured freedom from clinical activity and lately NEDA is the target for new clinical trials. This does include no relapses, no EDSS progression and no MRI activity. As we still are desperately searching for a meaningful impact of treatment on disease progression and long term placebo controlled clinical trials are not only financially unrealistic but also unethical, the PPV of a clinical outcome measure like NEDA on long term disability becomes very important. This clinical outcome measurement is finally what patients want to see and is as close to cure as we can get.

Reference: JAMA Neurol 2015 Feb 1;72(2):152-8
Abstract

Vaccines and the risk of multiple sclerosis and other central nervous system demyelinating diseases

Authors: Langer-Gould A et al

Summary: These researchers conducted a nested case-control study using electronic health records to investigate whether vaccines increased the risk of MS or other acquired central nervous system demyelinating syndromes (CNS ADS). The study cohort consisted of 780 incident cases of CNS ADS and 3885 controls. The researchers concluded there were no associations between hepatitis B vaccination (HBV) (odds ratio [OR], 1.12; 95% CI, 0.72-1.73), human papillomavirus vaccination (HPV) (OR, 1.05; 95% CI, 0.62-1.78), or any vaccination (OR, 1.03; 95% CI, 0.86-1.22) and the risk of CNS ADS up to 3 years later. They also found vaccination of any type was associated with an increased risk of CNS ADS onset within the first 30 days after vaccination (OR, 2.32; 95% CI, 1.18-4.57).

Comment: Case reports of MS following vaccination with HPV raised some criticism about the recently rolled out school program for this vaccination. This study tries to reassure us but I am not quite sure if they succeeded. Previously HBV was found to be associated with acute demyelination. Therefore the study concentrates on HBV and HPV vaccinations. The authors were able to select their index cases from a large population: 3.5 milllion members of an insurance company. They also selected for each index case 5 matched controls. There was no long term risk of demyelination associated with vaccination, but there seemed to be a statistically non significant trend towards presentation with MS within 42d after vaccination. This represents more an unmasking of autoimmunity rather than an increased risk per se. It was also of note that the cases had more visits to a health care provider for infections in the prior 6 months. This just confirms that any infection and potentially vaccination can activate already primed T cells.

Reference: JAMA Neurol 2014 Dec;71(12):1506-13
Abstract

Relationships between quantitative spinal cord MRI and retinal layers in multiple sclerosis

Authors: Oh J et al

Summary: Modern disease modifying treatments (DMTs) are very good in suppressing inflammation in the brain. Unfortunately there is ongoing disease progression which is far more difficult to measure. Recent studies have tried to capture this disease progression which is not entirely independent from inflammation by measuring brain atrophy. Many clinical trials have demonstrated what is commonly called “pseudoatrophy” within the first year of treatment when inflammation is dramatically reduced resulting in a decrease of total brain volume. There were some suggestions that ocular computer tomography (OCT) is more indicative of this progressive axonal loss than total brain volume measurements with its inherent variability to multiple factors. This study now tries to prove that OCT is indeed a valid measure of the global process rather than axonal loss within the visual pathway alone. They found significant associations in their 102 patients between retinal nerve fibre layer (RNFL) and spinal cord atrophy measured by cross sectional area (CSA) and diffusion-tensor imaging (DTI). This association was stronger for progressive patients than relapsing remitting patients and not found in a small number of healthy controls. Not surprisingly, spinal cord CSA correlated closely with EDSS and vibration and OCT with visual acuity. Brain parenchymal fraction only correlated with MS functional composite.

Comment: Unfortunately this study has not succeeded to demonstrate that we can replace the expensive and time-consuming monitoring of brain MRI by OCT but rather using this tool in conjunction with brain MRI and spinal cord measurements.

Reference: Neurology 2015 Feb 17;84(7):720-8
Abstract

Selection of papers and comments are provided by A/Prof Jeannette Lechner-Scott.

Associate Professor Jeannette Lechner-Scott is currently a senior staff specialist at the John Hunter Hospital in Newcastle, Australia.

She graduated from University of Heidelberg in Germany in 1990 and finished her PhD on pain pathways in the rat in 1991. She trained at the University Hospitals of Freiburg and Basel. In Basel she was part of one of the largest Multiple Sclerosis centres in Europe under the guidance of Prof. Ludwig Kappos with whom she developed a distance assessment scheme for MS known as EDSS by phone as well as a training program, which has become the standard scoring system of MS disability for every clinical trial and is easily accessible on the net. Since 2006 she has initiated a multidisciplinary MS clinic for Northern New South Wales caring currently for about 600 people with MS. She is principal investigator of numerous clinical trials and has published on epidemiological, neuro-psychological and genetic projects. She is chair of the MSRA clinical trials network and member of the ANZGene collaboration as well as board member of several advisory committees.

Correlation between brain volume loss and clinical and MRI outcomes in multiple sclerosis

Authors: Radue EW et al

Summary: This post hoc analyses of the phase 3 trials of fingolimod (FREEDOMS, FREEDOMS II, and TRANSFORMS) investigated the determinants and clinical correlations of MRI-detected brain volume loss (BVL) among patients with relapsing-remitting MS. The authors concluded the rate of BVL in patients during the fingolimod trials correlated with disease severity at baseline and new disease activity on study, and was associated with worsening disability.

Comment: The clinical trials with fingolimod were the first to demonstrate a significant reduction of BVL on treatment compared to not only placebo but also beta-IFN 1a im. This difference was already apparent after 6 months. This study now combines all pivotal clinical trials with fingolimod and looks at the clinical correlations of BVL. BVL was independent from gender in this large study of 3635 patients when measured with SIENA in 2D 3 mm slices, followed up for 4 years. BVL was clearly dependent on T2 lesion volume and Gd enhancing lesion count at baseline. This indicates that ongoing inflammation is the driver of brain atrophy. It also demonstrated a correlation of BVL with EDSS and confirmed disease progression although I am not entirely clear if this was statistically significant. This meta-analysis underlines the importance of inflammation in brain volume loss.

Reference: Neurology. 2015 Feb 24;84(8):784-93
Abstract

Reduced information processing speed as primum movens for cognitive decline in MS

Authors: Van Schependom J et al

Summary: The time course of decline of different cognitive domains was assessed using neuropsychological data from 514 MS patients. Testing included the Neuropsychological Screening Battery for MS (NSBMS) and the Symbol Digit Modalities Test (SDMT). The authors reported survival curves of tests focusing on information processing speed declined significantly faster than tests with less specific demands of information processing speed.

Comment: Cognitive decline is an important symptom of MS, which occurs already in early disease and has major implications for patients' quality of life. Up until recently it has been neglected as outcome measure in clinical trials. Even the trials that assessed treatment effect on cognition in hindsight only found an improved learning effect rather than cognitive decline clearly observed in the clinical setting. This study is now trying to assess which is the most sensitive test for change by using survival analysis. Of the large cohort of 514 MS patients not everybody had a follow up test, so it is not quite clear if this is a cross sectional or longitudinal study. They claim no learning effect as tests are only done every 2 years. The data is derived from a rehabilitation centre, effect of rehabilitation though has not been assessed. Factors influencing decline are age at onset and disease duration. As progressive patients have a later age at onset they decline at a later age than relapsing remitting patients. This study confirms that information processing speed is more effected by MS than memory and that SDMT is an excellent tool to monitor the disease progression.

Reference: Mult Scler 2015 Jan;21(1):83-91
Abstract

Thalamus structure and function determine severity of cognitive impairment in multiple sclerosis

Authors: Schoonheim MM et al

Summary: The study cohort of 157 patients with MS 6 years postdiagnosis, was divided into 3 groups: cognitively preserved (n = 108), mildly cognitively impaired (n = 22), and more severely cognitively impaired (n = 27) and matched to healthy controls (n=47). The group reported thalamic volume was significantly lower in all patient groups compared to controls. The lowest volumes were in patients with more severe cognitive impairment, and there were no differences between cognitively preserved and mildly cognitively impaired. They also noted increased thalamic functional connectivity only became apparent in the severely cognitively impaired group.

Comment: Recently, new MRI techniques have been utilised to explain the process that leads to cognitive decline in MS patients. Thalamic atrophy has been found to be more closely linked to cognitive function than total BVL. This study of 157 relapsing remitting patients with around 6 years of disease duration confirmed previous studies linking severe cognitive impairment with reduced thalamic volume, increased mean diffusivity as measured by DTI and increased connectivity as measured by fMRI. Volume loss and increased diffusivity is an indication of axonal loss. How this correlates with increased connectivity is still unclear. You would expect and it has previously been described that increased connectivity translates into better function. The authors postulate that as these findings are from a cohort with early disease, in a later disease stage we might see decreased connectivity. We definitely need more longitudinal studies to make sense out of these new MRI findings.

Reference: Neurology 2015 Feb 24;84(8):776-83
Abstract

High-dose immunosuppressive therapy and autologous hematopoietic cell transplantation for relapsing-remitting multiple sclerosis (HALT-MS): A 3-year interim report

Authors: Nash RA et al

Summary: Stem cell therapy receives enormous media attention in contrast to the paucity of properly conducted trials. As with previous reports in haematopoietic stem cell transplantation (HSCT) this single arm phase 2 trial of 25 patients lacks the scrutiny expected from pharmaceutical trials. Despite the seriousness of the intervention, assessments were done only every 6 months for the first 2 years and annually thereafter. Only grade 3 and 4 adverse events were recorded. More than half of the patients had serious infections. 2 deaths occurred during the study period, one due to MS progression. One died of worsening asthma. Although these deaths occurred more than 2 years after treatment, the fact is that CD4 cells hadn't recovered even after 2 years. This clearly outlines an effect of the treatment for more than 2 years. These serious adverse events explain the high drop out rate of 20% at 1 year and 33% at 3 years.

Comment: The reported success rate of no disease activity at 3 years in 86% of participants is difficult to comprehend based on the information given and should not be compared to a placebo controlled trial. Although there is no doubt that HSCT is an effective treatment, multicentre controlled trials need to be conducted before a treatment with such high morbidity and mortality risk is offered to patients, even those with active disease.

Reference: JAMA Neurol 2015 Feb 1;72(2):159-69
Abstract

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