Multiple Sclerosis Research Review™

Making Education Easy

Issue 5 – 2015

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Abbreviations used in this review:

beta-IFN = beta-interferon;
BREMSO = Bayesian Risk Estimate for MS at Onset;
CDMS = clinically-definite multiple sclerosis; **CIS** = clinically isolated syndrome;
CMV = cytomegalovirus; **CSF** = cerebrospinal fluid;
DWI = diffusion weighted imaging; **EBV** = Epstein–Barr virus;
EDSS = Expanded Disability Status Scale; **GA** = glatiramer acetate;
IRIS = immune reconstitution inflammatory syndrome;
MS = multiple sclerosis; **NFL** = neurofilament light protein;
OCB = oligoclonal bands; **PML** = progressive multifocal leukoencephalopathy;
RRMS = relapsing remitting multiple sclerosis;
SPMS = secondary-progressive multiple sclerosis;
SSRIs = selective serotonin-reuptake inhibitors.

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Welcome to the fifth issue of Multiple Sclerosis Research Review.

Researchers analysing MRI patterns in natalizumab-associated progressive multifocal leukoencephalopathy manifestations reported a rather localised disease, frequently located in the frontal lobes, affecting the cortical grey matter and adjacent juxtacortical white matter. Another paper reports initiating fingolimod therapy 8-12 weeks after natalizumab discontinuation is associated with a lower risk of disease reactivation than initiation after 16-week washout. A posthoc analysis of fingolimod first-dose effects in relapsing multiple sclerosis patients found co-administration of SSRIs was not associated with an increased incidence of any electrocardiogram findings compared with fingolimod therapy alone.

A large multicentre study concluded MRI lesion load, oligoclonal bands and age at clinically isolated syndrome as the strongest independent predictors of conversion to clinically-definite multiple sclerosis. Another study included in this issue confirms the use of CSF neurofilament light protein as a biomarker in MS. An observational study reports on a simple tool, which can be used in the early stages of MS to predict its evolution. This issue concludes with an important study that found fatigue was an independent predictor of a subsequent diagnosis of MS. A major problem remains that we do not have an objective tool to measure fatigue.

I hope you find the research in this issue useful to you in your practice and I look forward to your comments and feedback.

Kind Regards,

Associate Professor Jeannette Lechner-Scott

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Cerebrospinal fluid immunological biomarkers associated with axonal damage in multiple sclerosis

Authors: Villar LM, et al

Summary: This study examined cerebrospinal fluid (CSF) of 127 relapsing remitting multiple sclerosis (RRMS) patients (only 28 of which fulfilled McDonald criteria at the time of lumbar puncture). It is a cross-sectional study comparing neurofilament light protein (NFL) levels in CSF of MS patients with non-inflammatory neurological diseases (n=37). A cut off level of 900 ng/l, 3STD higher than the mean level in the control group, was determined. Only 72 out of the 127 MS patients were above this threshold, but had significantly higher Multiple Sclerosis Severity Score and MRI activity marker (No of T2 lesions, No of Gd enhancing lesions and No of T1 lesions).

Comment: This is a further study confirming the use of CSF NFL as a biomarker, although not specific - it is also elevated in other neurodegenerative diseases. It is not only a marker of inflammation but also of axonal damage as indicated by the elevated T1 "black wholes" in the higher NFL group. Another interesting aspect of this study is the close correlation of a higher NFL with B-cells and particular IgM positive oligoclonal bands (OCB). These markers could be assessed at diagnosis and aid in treatment choices, although the predictive value of these markers still needs to be proven. Some effort has gone into measuring NFL in serum, as repeated lumbar punctures are not a practical solution to monitor disease activity.

Reference: Eur J Neurol 2015 Aug;22(8):1169-75

Abstract

MRI pattern in asymptomatic natalizumab-associated PML

Authors: Wattjes MP, et al

Summary: This team analysed MRI sequences of 18 MS patients with natalizumab-associated progressive multifocal leukoencephalopathy (PML) lesions for lesion distribution, appearance, grey matter/white matter involvement and possible signs of inflammation. The team concluded a classical imaging pattern was observed in 44.4% of patients including unilateral and unilobar focal lesions in the frontal lobe affecting the cortical grey matter or the cortical grey and adjacent white matter. Signs of inflammation were detected in 38.8% of patients.

Comment: With the introduction of more effective treatments for MS the neurologist will have to shift his attention more often monitoring side effects. PML is a serious side effect of natalizumab and has as per September update affected 588 patients treated with natalizumab (per 142,000 patients treated worldwide). The current recommendations are to test JCV-antibodies 6 monthly and in JCV-antibody positive patients MRI 3-6 monthly. There is clear evidence that patients detected early on MRI without clinical evidence of PML have a better outcome. Therefore being aware of the MRI characteristics of PML early in the piece is not only important for radiologists but also neurologists. This article describes 18 asymptomatic patients where PML was diagnosed consequently. These patients had predominantly frontal lobe lesions, involving subcortical and juxtacortical white matter but also adjacent grey matter. 30% showed contrast enhancement. Although DWI has been advocated as typical for PML, 40% in this cohort did not show any high signal intensity on diffusion weighted imaging (DWI) sequences. Small, punctate T2 hyperintensities or punctate enhancement can be an early sign of immune reconstitution inflammatory syndrome (IRIS). It is important to familiarise oneself with these images to be able to detect PML early as it is occurring not only in patients treated with natalizumab but also oral therapies.

Reference: J Neurol Neurosurg Psychiatry 2015 Jul;86(7):793-8
Abstract

Fingolimod first-dose effects in patients with relapsing multiple sclerosis concomitantly receiving selective serotonin-reuptake inhibitors

Authors: Bermel RA, et al

Summary: This posthoc analysis compared cardiac outcomes in over 3,300 patients with relapsing multiple sclerosis who were or were not receiving selective serotonin-reuptake inhibitors (SSRIs), during fingolimod treatment initiation. The authors concluded co-administration of SSRIs and fingolimod was not associated with an increased incidence of any electrocardiogram findings compared with fingolimod therapy alone.

Comment: There has been a recent warning added to the Australian prescriber guidelines about the concomitant use of fingolimod and SSRI, particularly citalopram and escitalopram. This poses a major problem for the clinician as a significant proportion of MS patients suffer from depression or anxiety and require treatment. This study is a subgroup analysis of all phase II and III clinical trials with fingolimod looking specifically at the first dose effect of fingolimod on patients receiving SSRIs. All 3,300 patients included in the study followed inclusion and exclusion criteria of the original studies, which means exclusion of patients with prolonged QT (>440ms) or any heart disease. Controlled hypertension and either calcium channel or beta blockers were allowed. Depression and anxiety are highly prevalent symptoms in MS and SSRIs are the preferred treatment, facts reflected in this large cohort. What this study shows is that SSRIs do increase the QT interval, but this is only minimally changed by fingolimod and certainly not resulting in any concerning clinical events. 85% were discharged 6 hours after first dose and having been on SSRI or not did not change this outcome nor the occurrence of first-degree heart block (3.4% vs. 4.6%). I would have liked to see absolute QT interval measurements and a statistical comparison, but obviously the numbers were too small. I doubt, though, we will ever see a controlled trial to resolve our concerns about the combination of the two drugs.

Reference: Mult Scler Relat Disord 2015 May;4(3):273-80
Abstract

BREMSO: A simple score to predict early natural course of multiple sclerosis

Authors: Bergamaschi R, et al

Summary: Disease course prediction becomes more and more important the more treatment choices there are. In this study the Bayesian Risk Estimate for MS at Onset (BREMSO) score was applied and correlated with time to onset of secondary progressive MS. The dataset used was the MSBase data from 2013 consisting of 20,925 MS patients from 55 MS centres from 25 countries around the world. Unfortunately 30% had to be excluded for not being RRMS or having missing data. A higher score was significantly associated with a shorter time to convert to secondary-progressive multiple sclerosis (SPMS) defined as Expanded Disability Status Scale (EDSS) progression by at least 1 point over 1 year.

Comment: The variables taken into account for the BREMSO score were restricted to age, gender and dysfunctional FS, but excluded important factors like relapse rate and MRI data. Such a risk score becomes more and more important in weighing up benefit and risks for treatment of MS, but it should probably include more factors like the ones explored in Tintore's paper.

Reference: Eur J Neurol 2015 Jun;22(6):981-9
Abstract

Defining high, medium and low impact prognostic factors for developing multiple sclerosis

Authors: Tintore M, et al

Summary: This study is one of the largest natural history studies reported following 1,015 patients with clinically isolated syndrome (CIS) for a mean of 81 months. The major advantage of this study over others is that it had MRIs available from 94% of the cohort, mostly done in one centre, and OCB from 78.6%. It clearly demonstrated that T2 lesion number is the strongest predictive factor not only for time to conversion to clinical definite MS (CDMS) but also for the percentage reaching an EDSS of 3.0. Only 9% with an initial normal MRI converted to McDonald criteria MS, even after this long follow up. Unlike previous studies positive OCB also had a high Hazard Ratio (1.3-2.8) to predict conversion to CDMS but also to reach an EDSS of 3.0. Gender did not reach statistical significance for conversion to CDMS or EDSS of 3.0 when measured as an independent prognostic marker, whereas younger age predicted relapses but had limited impact on disability.

Comment: As this was not a controlled trial the use of disease modifying therapies did not show any impact on conversion to CDMS but did on disability. It will be interesting to mine this data further with regards to time to reach disability score of 3 and even better 6.

Reference: Brain 2015 Jul;138(Pt 7):1863-74
Abstract

Conversion from clinically isolated syndrome to multiple sclerosis: A large multicentre study

Authors: Kuhle J, et al

Comment: This is a similarly large study as the one from Tintore following 1,047 CIS cases over a median of about 4 years. They used Poser criteria as definition of the end point, conversion to CDMS. 60% converted to CDMS in on average 14 months. They found similar predictors as the Spanish study, but rated positive OCB the highest (HR 2.18), similar to having more than 9 T2 lesions. Age, OCB and T2 lesion numbers were independent predictors, but OCB status was closely correlated with the T2 lesion number. Interestingly, although a strong predictive factor, 60% of the non converters were OCB positive. Although they adjusted for seasonal variation, Vitamin D levels did not reach statistical significance in the regression model. Similarly, location of relapse did not reach statistical significance. They found no impact of other environmental factors like Epstein–Barr virus (EBV) and cytomegalovirus (CMV) antibody status or smoking on conversion to CDMS, but an association of EBV but not CMV antibody status with OCB indicating that EBV might initiate B cell activation in CSF.

Comment: When translating this into clinical practice one has to be cautious as even OCB negative patients with 0-1 T2 lesions convert to CDMS in 21% of cases after 5 years. This data set will also need to be mined for predictors of disability outcome after 5 year follow up, which I am sure we will see in the near future.

Reference: Mult Scler 2015 Jul;21(8):1013-24
Abstract

Switching from natalizumab to fingolimod: A randomized, placebo-controlled study in RRMS

Authors: Kappos L, et al

Summary: This study aimed to answer the question how long the wash out period should be when switching from natalizumab to fingolimod with regards to a potential rebound effect of the drug. Patients were assigned to 8, 12 or 16 weeks interval with 4 weekly MRI up to week 24. The study included 112 patients, substantially less than planned (600), which left only 41, 31 and 40 patients per treatment group resulting in less T2 lesion load in the 16 weeks group and less exposure in the 12 weeks group. Reason for switching in 50-60% of patients was positive JCV antibody. The primary outcome, mean number of active T2 lesions, was higher in the 16 weeks than the 12 and 8 weeks treatment group, whereas the clinical outcome, relapses, was not significant but showed the same trend due to the small number of patients enrolled.

Comment: The study was too small to show any significant differences in the safety outcomes, but there seemed to be a higher rate of infections (predominantly urinary tract infections and sinusitis) in the 8 weeks treatment group. The authors suggest an optimal interval between 8-12 weeks for switching between natalizumab and fingolimod due to the overlap of actions within 3 months of stopping natalizumab based on the receptor occupancy.

Reference: Neurology 2015 Jul 7;85(1):29-39
Abstract

Peginterferon beta-1a in multiple sclerosis: 2-year results from ADVANCE

Authors: Kieseier BC, et al

Summary: ADVANCE is a large study (n=1,512) that for the first year randomised to placebo, 2 weekly or 4 weekly subcutaneous pegylated beta-interferon (beta-IFN). After 1 year the ARR was 0.397 vs 0.256 vs 0.288 respectively which confirms that beta-IFN can reduce ARR by 1/3. This publication now describes the 2 year data, where the placebo group was randomised to 2 or 4 weekly injections. Interestingly the ARR reduced further to 0.178 in the 2 weekly injection group whereas it stayed the same in the 4 weekly group. A similar effect was observed on new T2 lesions. There were 12% dropouts and data was analysed from the intention to treat population. When comparing the 2 weekly injection group vs delayed treatment group they demonstrated a 30% reduction in 3 and 6m disability progression. Comparing 2 and 4 weekly injections does not really make sense as we know that activity levels of pegylated IFN 1a lasts less than 10 days. It would have been nice to have NEDA and brain atrophy data to be able to compare this study to current new therapies.

Comment: It is getting increasingly difficult to convince patients to start on an injectable therapy while the evidence of efficacy for oral and intravenous therapies accumulates. A more convenient 2 weekly subcutaneous injection makes beta-IFN acceptable for new onset patients but evidence of efficacy needs to be comparable to other therapies.

Reference: Mult Scler 2015 Jul;21(8):1025-35
Abstract

GLACIER: An open-label, randomized, multicenter study to assess the safety and tolerability of glatiramer acetate 40 mg three-times weekly versus 20 mg daily in patients with relapsing-remitting multiple sclerosis

Authors: Wolinsky JS, et al

Summary: These researchers evaluated the safety and tolerability when converting from glatiramer acetate (GA) 20 mg/mL once-daily subcutaneous injections (GA20) to GA 40 mg/mL three-times weekly (GA40) in 209 RRMS patients. The authors reported the adjusted mean annualised rate of injection-related adverse events was reduced by 50% with GA40 versus GA20. They also reported a 60% reduction in the rate of moderate/severe events.

Comment: Glatiramer acetate has a substantial body of evidence around drug safety after 2 million patient years of experience. The main concern has been the injection site reaction and lipoatrophy after years of injections. Reducing the number of injections surely had to result in a decrease of these side effects. After having proven with the GALA study that GA 40mg/ml second daily is equivalent in efficacy to 20mg/ml daily this study now looks at switching from one preparation to the other. It is not surprising to see that injection related adverse events as well as injection site reactions halved in the GA40 group. There was more bruising in the GA20 group (5.4 vs 0.2%). Of concern is that 4 out of 108 patients report skin necrosis after 4 months in the GA40 group (none in the GA20 group). There were improved convenience scores in the GA40 group but no statistically significant difference in change of scores.

Reference: Mult Scler Relat Disord 2015 Jul;4(4):370-6
Abstract

Fatigue at time of CIS is an independent predictor of a subsequent diagnosis of multiple sclerosis

Authors: Runia TF, et al

Summary: This is an important study especially in view of discussions about including fatigue into NEDA criteria. In a cohort of 127 CIS cases fatigue was assessed as a possible independent predictor for conversion to CDMS. 41% of patients converted to CDMS in on average 21 months. 46.5% of CIS patients suffered fatigue compared to 5.3% of the healthy controls (n=57). Fatigue scores were not associated with age, gender, localisation of symptoms, MRI or Vitamin D. Not only was fatigue score above 5 associated with conversion to CDMS (HR of 4.5) but also with time to conversion, which confirms its impact. The only other significant predictor of CDMS was multifocal onset (HR 3.2).

Comment: This is an important study to demonstrate how important fatigue is for the disease course of MS. A major problem remains that we only have questionnaires to measure it and no objective tool. Also, the biological basis of fatigue is still elusive.

Reference: J Neurol Neurosurg Psychiatry 2015 May;86(5):543-6
Abstract

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Selection of papers and comments are provided by Associate Professor Jeannette Lechner-Scott.

Jeannette Lechner-Scott graduated at University of Heidelberg in Germany, where she also completed her PhD about pain pathways. She trained in Neurology in Freiburg, Germany and Basel, Switzerland, where she worked with Ludwig Kappos at one of the major MS centres in Europe. She developed together with Ludwig Kappos a training scheme for EDSS assessment as well as a tool for assessment over the phone. She is currently head of the MS clinic in the John Hunter Hospital in Newcastle caring for about 700 patients in the area. Her research interests are the genetics and epigenetics of MS as well as cognitive impairment in MS.

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