Neurology RESEARCH REVIEW™

SUPPLEMENT: MULTIPLE SCLEROSIS

Making Education Easy

Issue 65 – 2020

In this issue:

Abbreviations used in this issue

CSF = cerebrospinal fluid
CNS = central nervous system
DMT = disease-modifying therapy
EDSS = Expanded Disability Status Scale
MOG = myelin oligodendrocyte glycoprotein
MRI = magnetic resonance imaging
MS = multiple sclerosis
pwMS = people with MS
RRMS = relapsing-remitting MS

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Welcome to this special issue of Neurology Research Review, focusing specifically on MS.

The emergence of COVID-19 and the subsequent pandemic present a unique challenge to neurologists managing patients with MS. As for the general population, most patients with MS will likely have only mild symptoms with COVID-19 infection, but some immunotherapies may increase the risk of more severe infection and individualised risk assessment is essential. This issue includes a number of studies (2 each from the UK and Italy) that discuss the management of MS patients during the COVID-19 era, as well as an interesting selection of other recently published MS studies.

We hope you find the selected studies interesting, and welcome your feedback.

Kind regards,

Dr Jennifer Pereira
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Treating multiple sclerosis and neuromyelitis optica spectrum disorder during the COVID-19 pandemic

Authors: Brownlee W et al.

Summary: This commentary highlights the implications of COVID-19 for people with MS and related neuroinflammatory disorders such as neuromyelitis optica spectrum disorder. In particular, it discusses the risk of respiratory infections in these patients, and gives general health advice and guideline-based recommendations for immunotherapies, relapse management and service delivery during the COVID-19 pandemic.

Comment: It is postulated, based on infection-related health care utilisation data, that pwMS are at greater risk from coronavirus but the degree of risk is not yet known. Recommendations and advice for patients and their treating neurologists were rapidly developed as the COVID-19 pandemic spread internationally. Registries to collect data regarding the risk of coronavirus for pwMS including those on DMT are underway. General principles, as outlined in this report are helpful but they then need to be applied to the individual. Practically, we have been encouraging pwMS to continue their MS treatment and follow WHO advice on preventative measures including hand hygiene and to work from home. Consultations have been undertaken by telephone, natalizumab dosing intervals have been extended, and we have delayed the starting and retreatments of ocrelizumab and considered alternatives to ocrelizumab where possible.

Reference: Neurology 2020; published online May 7
Abstract

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The COVID-19 pandemic and the use of MS disease-modifying therapies

Authors: Giovannoni G et al.

Summary: The Italian Society of Neurology has produced recommendations for the management of patients with MS during the COVID-19 pandemic. The guidelines provide advice on how to manage patients in the short-term, but do not address supervision of these patients in the intermediate or long-term especially those with highly active disease. Given the lack of knowledge or data on the COVID-19 disease course in MS patients receiving DMTs, there is at present no recommendation to stop DMTs and expose patients to the risk of MS exacerbations. Any decisions about 'lymphodepleting' DMTs should be based on individual circumstances. In patients with confirmed COVID-19 infection, any first or second-line DMT should be withheld until clinical resolution and an infectious disease specialist has approved continuation of treatment.

Comment: This commentary by Professor Giovannoni et al. is well thought out and addresses the current management issues for pwMS who are on or starting DMTs during COVID-19. The authors weigh up the potential risk of the virus against the risk of withholding treatments leading to inadequate MS disease control. They state there is no clear evidence, only scientific principles to guide us in the balancing of this. They advocate for the implementation of high efficacy drugs where indicated based on evidence in the literature "in conjunction with appropriate behavioural modification to reduce and ideally prevent exposure to the virus". They acknowledge these decisions need to be individualised and include details of the multiple factors to consider in each patient's case e.g. type of immunotherapy, co-morbidities, smoking, ambulatory status, age, weight, history of respiratory illness, as well as the requirement for hospital attendance for infusion, MRI and clinical monitoring. COVID-19 MS registries will give a better understanding of the risk we are attempting to mitigate – but for now the appropriate balance for an individual is an informed decision based on limited data.

Reference: Mult Scler Relat Disord 2020;39:102073
Abstract

COVID-19 in a MS patient treated with ocrelizumab: Does immunosuppression have a protective role?

Authors: Novi G et al.

Summary: This case report described a patient who developed COVID-19 while being treated with the B-cell depleting monoclonal antibody ocrelizumab for primary progressive MS. Despite complete B cell depletion, the patient's symptoms abated several days after hospitalisation, and he was discharged. Follow-up phone interview 2 weeks later confirmed that no new symptoms had developed.

Comment: The cytokine storm that accompanies coronavirus infection contributes to the severe pulmonary disease seen in individuals requiring intensive care unit support. There has also been a published case report of acute necrotising encephalopathy due to blood-brain barrier breakdown also due to the effect of cytokine release complicating this viral infection. Immunotherapy may protect against these parainfectious phenomena but it is not possible to conclude if the theoretical advantage of a reduction in these is of greater benefit to the prompt eradication the virus.

Reference: Mult Scler Relat Disord 2020; published online Apr 15
Abstract

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Digital triage for people with multiple sclerosis in the age of COVID-19 pandemic

Authors: Bonavita S et al.

Summary: This article described the development of a digital triage tool for the remote monitoring of infection risk in people with MS (especially those being treated with immunosuppressants) during the COVID-19 pandemic. The tool can be sent to patients to identify those with a high risk of COVID-19 infection. This should limit unnecessary visits to MS centres, and reduce the risk of spreading the infection.

Comment: The use of digital technology during the coronavirus pandemic can be used to minimise the risk that a health professional/hospital visit poses to an individual at high risk of coronavirus-related morbidity/mortality. This is a tool for digital triage that identifies those pwMS at risk of actually having coronavirus but it could be adapted to identify those at greater risk from the virus also.

Reference: Neurol Sci 2020;41(5):1007-9
Abstract

Blood neurofilament light levels segregate treatment effects in multiple sclerosis

Authors: Delcoigne B et al.

Summary: This study evaluated changes in plasma neurofilament light chain (pNfL) levels in patients receiving DMTs for RRMS. Blood samples and long-term clinical follow-up data were analysed for 1261 Swedish patients with RRMS who started treatment with a novel DMT (alemtuzumab, dimethyl fumarate, fingolimod, natalizumab, rituximab, or teriflunomide). Baseline pNfL levels were found to be positively associated with relapse rate, EDSS score, Age-Related MS Severity Score, and MS Impact Score, and negatively associated with Symbol Digit Modalities Test performance and the number of previously used DMTs. Both the reduction in pNfL levels from baseline to on-treatment measurement and the on-treatment pNfL levels differed across DMTs. For example, patients starting alemtuzumab had the highest reduction in pNfL levels and the lowest on-treatment pNfL levels, while those starting teriflunomide had the smallest decrease and highest on-treatment levels.

Comment: Our current method to track the response of MS disease to a given DMT is clinical (new relapses or progressive disability on history and exam) and radiological (new or enlarging lesions or atrophy on MRI of the brain and spine). These are helpful but given the increasing numbers of different treatments with varying levels of efficacy and risk, additional data provided through biomarkers such as pNfL would help to better inform the need to augment therapy.

Reference: Neurology 2020;94(11):e1201-12
Abstract

Independent commentary by Dr Jennifer Pereira BHB, MBChB, FRACP, MD

After undergraduate training in medicine at the University of Auckland, Jennifer trained in neurology at Auckland City Hospital. Postgraduate training consisted of an MS research fellowship, with the Therapeutic Immunology Group in the Department of Clinical Neurosciences, University of Cambridge (UK). **For full bio CLICK HERE**

Cerebrospinal fluid kappa and lambda free light chains in oligoclonal band-negative patients with suspected multiple sclerosis

Authors: Ferraro D et al.

Summary: CSF kappa free light chains (FLCs) may be a more sensitive marker of intrathecal IgG synthesis than oligoclonal bands (OCBs). This study determined the additional value of the kappa and lambda index (CSF FLC/serum FLC)/(CSF albumin/serum albumin) for predicting an MS diagnosis in OCB-negative patients with suspected MS. 391 OCB-negative patients with suspected/possible MS and 54 OCB-positive patients with MS had their CSF tested for serum kappa and lambda FLCs. CSF kappa FLC levels were below the limit of detection (0.27 mg/L) in 61% of patients. The best kappa index cut-off value for the prediction of MS was determined to be 5.8. A kappa index ≥5.8 was present in 25% of OCB-negative patients with suspected MS and 98% of OCB-positive patients with MS. 24% of OCB-negative patients with MS had a kappa index ≥5.9, compared with 5.4% of OCB-negative patients without MS (p<0.001). No reliable data could be obtained for the lambda index because lambda FLC levels were below the limit of detection (0.68 mg/L) in 90% of CSF samples.

Comment: OCB and FLC synthesis both demonstrate the same immunological phenomenon in CSF. They reflect the activation of intrathecal plasma cell clones and so neither OCB nor FLC are specific to MS disease. The presence of OCBs in the CSF supports the diagnosis of MS. It is important to carefully consider the differential diagnosis if the CSF is negative for OCB. This is especially the case if the CSF was performed for an atypical clinical or radiological presentation – OCB are negative in those with aquaporin 4 or MOG-associated demyelination.

Reference: Eur J Neurol 2020;27(3):461-7
Abstract

Infection risks among patients with multiple sclerosis treated with fingolimod, natalizumab, rituximab, and injectable therapies

Authors: Luna G et al.

Summary: This nationwide register-based cohort study in Sweden examined the risk of serious infections associated with DMTs for MS. All patients with RRMS who were recorded in the Swedish MS register as initiating treatment with a DMT (rituximab, natalizumab, and fingolimod or the injectable therapies interferon beta and glatiramer acetate) were age- and sex-matched with a general population comparator cohort. A total of 6421 patients were included, plus a comparator cohort of 42,645 individuals. The crude rate of serious infections resulting in hospitalisation was higher in patients with MS taking interferon beta and glatiramer acetate than the general population (incidence rate, 8.9 vs 5.2 per 1000 person-years), and higher still in patients taking fingolimod (14.3 per 1000 person-years), natalizumab (11.4 per 1000 person-years), and rituximab (19.7 per 1000 person-years). After adjustment for confounding factors, the rate remained significantly higher for rituximab (hazard ratio, 1.70; 95% CI 1.11–2.61) but not for fingolimod or natalizumab compared with interferon beta and glatiramer acetate.

Comment: This observational study from Sweden offers real world registry data to inform our understanding of infections complicating rituximab, fingolimod, natalizumab and injectable therapies. It supplements knowledge from the original randomised controlled trials and is potentially informative when weighing up the risk of MS treatments in the setting of the coronavirus pandemic. An increased risk of infection for individuals with MS on DMTs compared to the general population is again confirmed. This risk varies according to the DMT, with the incidence in those on rituximab at 19.7 per 1000 person-years being the highest of the DMTs studied when compared to the general population (5.2 per 1000 person-years).

Reference: JAMA Neurol 2020;77(2):184-91
Abstract

Association between breastfeeding and postpartum multiple sclerosis relapses

Authors: Krysko KM et al.

Summary: This systematic review and meta-analysis evaluated the impact of breastfeeding on postpartum MS relapses. A search of PubMed and Embase identified 24 studies (n=2974) that satisfied eligibility criteria. The pooled summary odds ratio for the association of breastfeeding with postpartum relapses was 0.63 (95% CI 0.45–0.88; p=0.006) compared with a reference of nonbreastfeeding. A stronger association was seen in studies of exclusive rather than nonexclusive breastfeeding, although both demonstrated an association.

Comment: The degree of protection from MS relapse from the hormonal changes that result from breastfeeding are difficult to accurately calculate due to confounding by a number of variables – MS disease severity, partial versus exclusive breastfeeding, and use of DMTs to name the most likely to impact. 30% of women relapse in the postpartum phase and breastfeeding may reduce this by up to 40%. Breastfeeding offers additional advantages and should be supported where possible but there remains a significant risk of relapse. A safe and effective DMT for women who are breastfeeding postpartum remains important.

Reference: JAMA Neurol 2020;77(3):327-38
Abstract

Infusion-related reactions during natalizumab treatment: Do we still need a post-infusion observation period?

Authors: Sacco R et al.

Summary: This study determined the frequency and severity of infusion-related reactions (IRRs) during and after natalizumab infusion in a clinical practice setting. A total of 11,133 natalizumab infusions received by 302 MS patients (68.9% females, median age 33.6 years, median EDSS 2.5) at 3 Swiss and 2 Italian tertiary MS centres were analysed. IRRs occurred in 24 (8%) patients during the natalizumab infusion and in 7 (2%) during the 1-h post-infusion period. Only 8 patients needed pharmacological treatment. Age, sex and history of allergies did not affect the risk of IRR.

Comment: Natalizumab is a humanised monoclonal antibody administered by intravenous infusion 4 to 6 weekly. The risk of an infusion reaction is quoted as 9% with 1–4% of these being hypersensitivity reactions requiring discontinuation of the treatment. Observation for 1h post-infusion is recommended due to this potential complication. Convincing individuals to stay for the advised extra hour of observation is challenging and patients often leave at the completion of the infusion. This study provides statistics to inform patients and their treating clinicians regarding the risk of not adhering to this. IRRs occur more frequently with the first few infusions and during the 1 hour of the actual infusion, rather than afterwards. 75% occurred during and 25% occurred after administration, representing 0.43% and 0.14% of infusions. The risk of an IRR after the fifth cycle was low (0.06%) compared to that during the first 4 infusions (0.83%).

Reference: Mult Scler Relat Disord 2020;38:101523
Abstract

Why do multiple sclerosis and migraine coexist?

Authors: Hamamcı M et al.

Summary: This study investigated factors associated with the coexistence of RRMS and migraine. 50 RRMS patients with migraine, 50 RRMS patients without migraine, and 50 healthy volunteers had levels of vitamin D, vitamin D-binding protein, vitamin D receptor, high-sensitivity C-reactive protein (hs-CRP), superoxide dismutase, catalase, glutathione peroxidase, total antioxidant status, total oxidant status, and Oxidative Stress Index measured. Compared with patients with MS but no migraine, patients with MS and migraine were found to have significantly lower levels of vitamin D and antioxidant enzymes, and significantly higher levels of oxidative stress and hs-CRP.

Comment: It is not uncommon in MS clinics for the treatment of migraine to be an important part of symptom management. A high number (20–80%) of pwMS also have migraine compared to 11.7% of the population. I had considered it likely that the migraines were being triggered by CNS damage from MS disease. The authors of this study analysed the cause for this association further, showing lower vitamin D levels and increased CRP and measures of oxidative stress in those with migraine and MS.

Reference: Mult Scler Relat Disord 2020;40:101946
Abstract