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Demyelinating Disorders 2

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Demyelinating Disorders 2
RGC-32 as a potential marker of relapse and response to treatment with glatiramer acetate in multiple sclerosis

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Background: We have previously shown that response gene to complement (RGC)-32 and FasL mRNA expression are significantly lower in the peripheral blood mononuclear cells (PBMCs) of multiple sclerosis (MS) patients during relapses than in stable patients.
Objectives: We have now investigated the combined roles of RGC-32, FasL, and CDC2 as possible biomarkers of relapse and predictors of response to glatiramer acetate (GA) treatment in relapsing-remitting MS patients.
Material and Methods: Over the course of 2 years, a cohort of 15 GA-treated MS patients was clinically monitored using the Expanded Disability Status Scale, and blood samples were collected at 0, 3, 6, and 12 months. Target gene mRNA expression was measured in patients' isolated PBMCs by real-time quantitative PCR.
Results: During relapses MS patients had a decreased expression of RGC-32 ($P < 0.0001$) and FasL ($P < 0.0005$) mRNA but no change in CDC2 when compared to stable MS patients. As compared to non-responders, responders to GA treatment had significantly higher mRNA levels of RGC-32 ($P < 0.0001$) and FasL ($P < 0.003$) but no change in CDC2. Receiver operating characteristic analysis was used to assess the predictive power of each putative biomarker. The predictive values of relapse were 90% for RGC-32, and 84% for FasL; the predictive values of responsiveness to GA treatment were 85% for RGC-32 and 85% for FasL.
Conclusion: Our data suggest that RGC-32 and FasL could serve as potential markers for the prediction of MS relapses and the evaluation of patients' response to GA therapy.

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Lithium induced amelioration of a rat model of multiple sclerosis through the suppression of glycogen synthase kinase (GSK)-3 signaling

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Background: Glycogen synthase kinase (GSK)-3 is one of important molecules in the course of cell activation in the central nervous system diseases.
Objective: The aim of this study was to evaluate whether lithium, an inhibitor of GSK-3 beta, ameliorates rat paralysis with acute monophasic experimental autoimmune encephalomyelitis (EAE).
Material and Methods: EAE was induced in Lewis rats through immunization of guinea pig myelin basic protein (MBP) and complete Freund's adjuvant. Lithium was administered in immunized rats.Tissues and sera of rats were collected for the cytokine assay and signals by western blot analysis and immunohistochemistry.
Results: Lithium treatment significantly delayed the onset of EAE paralysis and ameliorated its severity compared with those of vehicle treated group.
Conclusion: Taken all into considerations, lithium, an inhibitor of GSK-3 beta, is a potential anti-inflammatory drug to suppress acute autoimmune diseases including rat EAE, possibly through the inactivation of GSK-3 signal cascades. (*supported by Basic Science Research Program through the National Research Foundation of Korea (NRF) funded by the Ministry of Education (Grant number: 2014R1A1A2055965)).

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Demyelinating Disorders 2
Microglial activation correlates with disease progression in multiple sclerosis

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Background: Activation of microglia is considered a crucial step in CNS response to injury. Measuring microglial activation *in vivo* is possible using PET imaging and radioligands binding to 18 kDa translocator protein (TSPO).
Objective: The aim of this cross-sectional study was to investigate how activation of microglia relates to certain milestones related to MS progression.
Patients and methods: MS patients with secondary progressive (SPMS,n = 10) or relapsing remitting (RRMS,n = 10) disease, and

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healthy controls (n = 8) were imaged using PET and the TSPO-binding radioligand ^{11}C-PK11195. Diffusion tensor imaging was performed for assessment of structural integrity of the normal appearing white matter (NAWM) tracts. In addition, we compaired the ex vivo tissue binding characteristics of PK11195 to immuno-stained cryosections of post mortem autopsy samples from progressive MS patients(n = 5).

Results: PK11195 binding was significantly increased in the perilesional white matter and in the NAWM of SPMS compared to RRMS patients ($p = 0.011$ and $p < 0.001$, respectively). A cut-off value of 1.02 in PK11195 binding in the NAWM separated the RRMS and SPMS groups from each other. The increased radioligand binding in perilesional WM and NAWM correlated to increasing clinical disability measured using EDSS ($p = 0.030$ and $p < 0.001$ respectively). In evaluation of tissue sections, there was increased rim-like perilesional PK11195 signal co-localised with increased microglial/macrophage activation around, but not within the chronic demyelinating lesions.

Conclusion: TSPO PET imaging can be used as a biomarker of diffuse neuroinflammation related to disease progression in MS, and can potentially be utilized to help identify patients entering the progressive phase of the disease.

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Demyelinating Disorders 2
Increased expression of miR-130b-5p in B cells and its modulation by glatiramer acetate in multiple sclerosis

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Objective/Background: B cells are implicated in the pathogenesis of multiple sclerosis (MS). Our objective was to identify microRNAs (miRNAs) expressed in B cells of MS patients applying Next Generation Sequencing (NGS), a high-throughput/sensitive tool to study disease pathogenesis, drug mechanisms, to discover new biomarkers and therapeutic targets.

Design/Methods: B cells and monocytes were separated from healthy donors (HD), untreated and Glatiramer Acetate (GA)-treated MS patients. Expression of more than 2500 mature human miRNAs annotated in miRBase 20 was tested by NGS and validated by RT-qPCR. IRB approval was granted.

Results: 370 and 443 miRNAs were detected in B cells and monocytes, respectively. In B cells and monocytes, respectively, expression of 21 and 12 miRNAs was significantly ($p < 0.05$) different in untreated MS patients compared to HD and expression of 19 and 13 miRNAs was different in GA-treated patients vs. untreated patients. The DIANA-mirPath software analysis identified that Adherent junction and Chemokine signaling (monocytes and B cells) and B cell receptor signaling (B cells) pathways are targets for these miRNAs. Expression of 3 miRNAs (miR-1295a, miR-450a-5p + 1, and miR-130b-5p) was increased in B cells of untreated MS patients and corrected/decreased by GA treatment. Expression levels of miR-130b-5p were increased by more than 100% in untreated MS patients compared to both HD and GA-treated patients based on both NGS and RT-qPCR results, $p < 0.05$.

Conclusion: Expression of miR-130b-5p in B cells is increased in MS patients and is corrected by GA treatment. The physiological significance of this finding will be discussed.

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Correlation between EDSS and cognitive decline in patients with multiple sclerosis. Pilot study of bicams version in a Brazilian population

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Background: Just like physical disability, the cognitive impairment occurs in a distressing form the patients with Multiple Sclerosis (MS). In addition to the routine approach to physical impairment, it is essential that a methodic and operational neuropsychological assessment be used, which definitely contributes in qualifying care of these patients. Reliable, validated and quick and easy applicable Neuropsychological Tests (TN) by Neurologist in routine visits, are essential tools for follow-up and to detect the need for future therapeutic intervention.

Objective: To investigate the correlation between clinical status of MS patients, measured by the EDSS, and the TN battery of BICAMS (International Brief Cognitive Assessment for Multiple Sclerosis).

Patients and Methods: Fourteen patients with a definitive diagnosis of Relapsing - Remitting MS (RRMS) were included. The results of the EDSS and TN of BICAMS (SDMT, CVLT-II and the BVMT) were obtained retrospectively from medical records of patients included. Pearson correlation coefficients *(r)* and coefficient of determination *(r^2)* were used to estimate the linear association between the variables. All included patients agreed to participate signed previously an Informed Consent Term.

Results: There was a great magnitude correlation between the EDSS, SDMT and BVMT, with $r = 0.69$ and 0.75 *($p < 0.05$)*, respectively. Although not reaching significance criteria, the EDSS and CVLT relationship was moderate and clinically substantial.

Conclusion: The Brazilian version of BICAMS seems to be of easy and satisfactory implementation in routine visit by Neurologists and presents clinically significant correlation with the EDSS. Future studies with wide extension should replicate these initial findings.

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Genetic variation among multiple sclerosis in Saudi patients

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Background: Pathogenesis of Multiple Sclerosis (MS) is poorly understood, available evidence suggests that both genetic and environmental components may play some roles.

Objectives: To study the genetic predisposition in familial MS in Saudi population.

Material and Methods: Whole Exome Sequencing (WES) was performed in multigeneration family members. Lifescope software was used for analysis which includes filtering low quality reads, alignment against reference genome (Hg19) and variant call. Variants

filtration was performed by in-house developed strategy between the subjects. SNPs and Indels were filtered to look for pathogenic mutations using public databases. In family, we filtered unique variants in the probands and unique shared sequence variants present in carrier parent and proband grandparent. Variants were confirmed by Sanger sequencing using specific designed primers.

Result: The exome sequence resulted in identification of 10,257 variants among 11 unaffected and seven affected family members of our familial MS based on the human reference genome (hg19), of which 1268 variants were found uniquely novels 35 variants were shared between affected members and predicted to have a deleterious or damaging effect. Mutation were confirmed by Sanger sequencing

Conclusion: We predicted involvement of 10 newly candidate genes from 35 new variants in Familial MS. Further studies are required on large cohort scale of familial and sporadic MS.

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Demyelinating Disorders 2
Association between soluble L-selectin and anti- JCV antibodies in natalizumabtreated relapsing-remitting MS patients

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Background: Long-term treatment of Natalizumab in relapsing-remitting MS (RRMS) patients is associated with the risk of developing progressive multifocal leukoencephalopathy (PML), a JC virus (JCV)-mediated disease of the CNS. Measurement of anti-JCV antibodies in natalizumab-treated MS patients is used for the estimation of patient's risk for PML and lower percentage of L-selectin CD4 + T cells has been suggested as a biomarker for individual PML risk assessment.

Objective: L-selectin is also present as functionally active soluble form in the blood upon shedding from the cell surface of activated T cells. Therefore, our aim was to examine whether the levels of soluble L-selectin (sL-selectin) can predict the risk of PML in natalizumab-treated RRMS patients.

Methods: The levels of sL-selectin and anti-JCV antibody indices in sera were measured from a total of 99 subjects of whom 44 RRMS patients were treated with natalizumab, 30 patients with IFN-β and 25 subjects were healthy controls.

Results: The significant correlation was found between the levels of sL-selectin and JCV-antibody indices in the natalizumab-treated patients ($r = 0.402$; $p = 0.007$; $n = 44$), but not in those treated with IFN-β. This correlation became even stronger in JCV-seropositive patients treated with natalizumab longer than 18 months therapy ($r = 0.529$; $p = 0.043$; $n = 15$). Moreover, significantly higher level of sL-selectin was detected in the high-risk group (JCV antibody index >1.5) compared to that with low risk group (JCV antibody index ≤1.5) for developing PML.

Conclusion: Our data suggest that the measurement of sL-selectin should be evaluated further as a potential biomarker for predicting the risk of developing PML.

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Demyelinating Disorders 2
Helicobacter pylori infection reduces disease severity in an experimental model of multiple sclerosis

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Background: Infection with Helicobacter pylori may reduce the risk of developing inflammatory diseases. The infection is also less common amongst patients with multiple sclerosis (MS), an inflammatory demyelinating disease of the central nervous system. However, there is no direct evidence that H. pylori is protective.

Objective: We aimed to investigate the impact of H. pylori infection on experimental autoimmune encephalomyelitis (EAE), an animal model for MS.

Design/methods: Groups of C57BL/6 mice were infected with H. pylori, or given the diluent alone as a placebo, prior to induction of EAE with myelin oligodendrocyte glycoprotein (MOG) peptide in CFA. Clinical scores were assessed and at termination of the experiment, tissues were harvested. CD4 + T-cell subsets were quantified by flow cytometry, and T-cell proliferation assays were performed.

Results: H. pylori infection significantly reduced the severity of EAE clinical scores and the proliferation of MOG peptide-specific T-cells in infected mice. There was a 4-fold reduction in the frequency of CD4 + cells in the CNS. CD4 + populations in both the CNS and the spleens of infected mice also contained greatly reduced proportions of IFNγ +, IL-17 +, T-bet +, and RORγt + cells. The frequencies of Foxp3 + cells were equivalent. There were no differences in the frequency of splenic CD4 + cells expressing markers of apoptosis between infected and uninfected animals.

Conclusions: H. pylori infection exerted some protection against EAE in mice, inhibiting both Th1 and Th17 responses. We provide experimental evidence to suggest that H. pylori may provide protection against immune-mediated diseases such as MS.

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Demyelinating Disorders 2
Absence of the anti-oxidant transcription factor Nrf2 exacerbates optic neuritis in a mouse model of multiple sclerosis

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Background: Optic neuritis is experienced by a majority of multiple sclerosis (MS) patients and is typically characterized by episodes of acute, monocular vision loss. These inflammatory episodes can lead to damage or degeneration of the retinal ganglion cells (RGCs) comprising the optic nerve (ON). Experimental autoimmune encephalomyelitis (EAE) is a well-established model of MS in which mice are immunized to produce a neuro-autoimmunity that recapitulates the cardinal hallmarks of the human disease, namely, increased oxidative stress, demyelination, and neurodegeneration.

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Objective: It has been previously demonstrated that mice deficient for the master anti-oxidant transcription factor Nrf2 are more susceptible to the motor deficits and spinal cord pathology induced by EAE. The goal of this study was to determine if Nrf2-deficient mice also exhibited exacerbated visual pathology in EAE.

Materials and Methods: EAE was induced in 8-week-old wildtype (WT) and Nrf2 knockout (KO) mice via immunization against MOG antigen. Visual acuity via optokinetic tracking (OKT) and motor deficits were assessed daily. Mice were harvested 21 days post-immunization. Retinas were flatmounted, immunostained, and RGCs were counted. ONs were paraffin-embedded and stained with H&E or immune cell-specific antibodies.

Results: Nrf2 KO mice exhibited more severe motor deficits, OKT decreases, RGC loss, and ON inflammation in response to EAE. This was not due to global differences in immune system development relative to WT mice.

Conclusion: Nrf2 plays a neuroprotective role in EAE-associated optic neuritis and may be an optimal therapeutic target to prevent RGC degeneration that leads to permanent visual impairment in MS patients.

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