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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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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 immunostained 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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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