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MicroRNA-484 and Apoptotic Protease Activating Factor-1 Gene in Relapsing Remitting Multiple Sclerosis: the Possible Interplay

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**Background:** Emerging evidence suggests that dysregulated apoptosis might be implicated in the pathogenesis of multiple sclerosis (MS). In this study we evaluated the expression of miR-484 and its potential target gene Apoptotic protease activating factor-1 (APAF-1) in relapsing remitting MS patients (RRMS), correlated their expression levels to patients’ clinical characteristics and investigated their role as potential disease biomarkers.

**Material(s) and Method(s):** After Bioinformatic analysis was conducted and revealed that APAF-1 is a potential target gene for miR-484. Reverse Transcription-quantitative Real-Time PCR (RT-qPCR) was performed to detect the expression levels of miR-484 and APAF-1 in the peripheral blood mononuclear cells (PBMCs) of 34 RRMS patients and 34 healthy controls.

**Result(s):** miR-484 expression was significantly upregulated in patients whereas APAF-1 mRNA was downregulated compared to controls (p < 0.01). APAF-1 mRNA expression was found to be significantly higher in treated patients (median RQ 1.2) compared to those who were not on treatment (median RQ 0.9) (P=0.02). Sensitivity and specificity of miR-484 and APAF-1 to diagnose MS were (88.2%, 86.7%) and (83.3% and 82.4%) respectively.

**Conclusion(s):** APAF-1 and miR-484 could play a role as promising therapeutic targets and potential diagnostic biomarkers.

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**Association of COVID-19 with Disability Progression and Disease Exacerbation in People with Relapsing-Remitting Multiple Sclerosis: Evidence from a Year-Long Observational Study**

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**Objective(s):** Neurological complications of COVID-19 have raised serious concerns among the experts, and hence, many mechanisms have been proposed to explain it. We sought to collect evidence by investigating the possible effect of the virus on multiple sclerosis (MS) disease course, in COVID-19-contracted people with relapsing-remitting multiple sclerosis (RRMS).

**Material(s) and Method(s):** This prospective-retrospective hybrid cohort study conducted from July 2020 until July 2021, compares the rates of probable disease progressions (PDP) and relapses between the pre- and post-COVID-19 periods of RRMS patients, using non-parametric tests, a matched binary logistic model offset by follow-up, Kaplan-Meier plots, and a cox regression model.

**Result(s):** The PDP rate (0.06 vs 0.19, P = 0.04) and relapse rate (0.21 vs 0.30, P = 0.30) were both lower in the post-COVID-19 period compared to the pre-COVID-19 period. However, matched binary logistic model offset by follow-up failed to display a significant difference in odds of PDP (OR [95% confidence interval]: 0.41 [0.13, 1.34], P = 0.14) and relapse (OR [95% confidence interval]: 0.99 [0.45, 2.17], P = 0.99), at the endpoints of pre- and post-COVID-19 periods. Kaplan-Meier plots and cox regression model did not show significant difference between the pre- and post-COVID-19 periods, regarding both the PDP rates (HR [95% CI]: 0.46 [0.12, 1.73], P = 0.25) and relapse rates (HR [95% CI]: 0.69 [0.31, 1.53], P = 0.36).

**Conclusion(s):** Our results suggest that COVID-19 contraction is unlikely to increase the risk of MS progression and relapse in the following months after infection.

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**Humoral Immune Response to SARS-CoV-2 Vaccination in MS Patients**

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**Objective(s):** The aim of this study was to study the humoral immune response to SARS-CoV-2 following vaccination in MS patients.

**Material(s) and Method(s):** We performed a prospective study including all MS patients receiving one of the approved COVID-19 vaccines since January to September 2021. Demographic characteristics, MS treatments and adverse events reports after COVID-19 vaccination of vaccinated MS patients were collected.

We analyzed the antibody response to SARS-CoV-2 vaccines with a chemiluminescent microparticle immunoassay (CMIA) from Abbot in MS patients with different DMTs at week 3, week 6 and month 3 after the first dose. The positivity cutoff is ≥50 AU/ml (manufacturer defined). 200 Healthy healthcare professionals were the control group.

**Result(s):** We analyzed 165 vaccinated MS patients: 106 with Pfizer, 14 with Moderna, 42 with both doses of Astra zeneca and 3 with Janssen. The mean age of patients was 45 (range: 21-71) and 46 for the controls. The most frequent adverse events were pain at injection site, headache and fatigue for 24-48 hours. No differences between MS patients and controls. No increased risk of relapse was noted in the first six months. 120 patients have received both doses of mRNA vaccine. Overall, mean antibody titers response to SARS-CoV-2 SARS-CoV-2 at three weeks was 7910,3 AU/ml (range 0-74947), at 6 weeks 16347,9 UA/ml (range0-52380,5) and at 3 months 8182,10 UA/ml (range0-33752,4) in mRNA vaccinated patients. By the mRNA vaccinated control group mean antibody titers response to SARS-CoV-2 SARS-CoV-2 at three weeks was 9397 AU/ml and at 6 weeks 18120 UA/ml.

Performing a subanalysis of the different DMTs: Only 3 out of 20 patients treated with ocrelizumab developed antibodies. Six vaccinated patients treated with rituximab had no antibody response. Four from 16 patients treated with fingolimod failed to develop a post-vaccination humoral response (< 50 AU/ml). 4 of 5 patients treated with ofatumumab developed have an adequate humoral response. Patients treated with interferon Beta, glatiramer acetate, teriflunomide, dimethyl fumarate, vaccinated with mRNA vaccines developed a similar post vaccination humoral response than healthy controls.

**Conclusion(s):** Most of MS treated patients developed enough antibodies to SARS-CoV-2. The adverse events on MS patients were similar to the general population. No increase of relapse activity was observed. Some patients treated with ocrelizumab, rituximab and fingolimod have no developed a humoral response to SARS-CoV-2 vaccination.

Hence we conclude that all approved COVID-19 vaccines are safe in MS patients and effective in most patients. However vaccine strategy in patients treated with anti-CD20 and fingolimod need further studies.

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