PROGRAM

Storebælt Sinatur Hotel & Konference
31. maj & 1. juni 2024

Nationalt MS Forskningsmøde 2024

- Afholdes i samarbejde med Dansk Multipel Sklerose Center
- MS Forskningstalent-priserne sponseres af Scleroseforeningen
- Mødet sponseres af Novartis, Sanofi, Alexion, Biogen, Merck og Roche.

DAREMUS

DANSK SELSKAB FOR FORSKNING I MULTIPEL SKLEROSE

Fredag 31. maj 2024

9:00-10:00	**Registrering og Kaffe/te med hjemmebagt brød**
10:00-10:10	**Velkomst ved DAREMUS' bestyrelse (Melinda Magyari)**
10:10-11:00	**DAREMUS lecture: (Chairs: Jeppe Romme Christensen & Nasrin Asgari)** Andrew Solomon, University of Vermont *"Multiple Sclerosis Differential Diagnosis - Contemporary Data and Updated Approaches"*
11:00-12:00	**MS Forskningstalent-priserne 2024 (Chairs: Melinda Magyari & Tobias Sejbæk)**
11.00-11.12	Frederik Elberling, RH *"Deeskalation af sygdomsmodificerende behandling i Danmark – et nationalt registerstudie"*
11.13-11.24	Tobias Gæmelke, AU *"Efficacy of Progressive Power Training in Enhancing Neuromuscular and Physical Function in Older Patients with Multiple Sclerosis"*
11.25-11.36	Sahla El Mahdaoui, RH *"Follikulære T-hjælper celler ved multipel sklerose og effekten af anti-CD20 behandling"*
11.37-11.48	Moschoula Passali, RH *"Cerebrospinal fluid neurofilament light chain as a biomarker for early diagnosis of multiple sclerosis in patients with optic neuritis"*
11.49-12.00	Mie Rye Wæde, OUH *"Hvordan påvirker anti-CD20-behandling immuncellerne i blodet hos multiple sklerose-patienter?"*
12:00-13:00	**Frokost**
13:00-14:30	**Videnskabelig session: Klinisk forskning (Chairs: Stig Præstekjær Cramer & Ronald Antulov)**
13.00-13.30	Keynote: Mads Alexander Madsen, Hvidovre Hospital *"Kortikale læsioner i multiple sklerose"*
13.30-13.42	Agata Bezcek, Roskilde *"Barriers to Clinical follow-up visits in multiple sclerosis: A Nationwide register-based study"*
13.43-13.54	Martin Langeskov-Christensen, Viborg *"Bad sleep = bad life? Sleep quality is clearly associated with quality of life in persons with MS - The Danish MS Hospitals Rehabilitation Study"*
13.55-14.06	Stig Præstekjær Cramer; RH *"Increased blood-brain barrier permeability in optic neuritis patients with early diagnosis of multiple sclerosis"*
14.07-14.18	Rolf Pringler Holm; RH *"Epidemiologisk indsigt i dansk multipel sklerose (1950-2024): Gennemsnitsalder, kønsfordeling, incidens og prævalens"*
14.19-14.30	Tobias Sejbæk; Esbjerg; *"Neurofilament light chain og glial fibrillary acidic protein er associeret med nye og/eller forstørrede T2 læsioner og hjerneatrofi"*

Program for DAREMUS nationalt forskningsmøde 2024 med de nyeste resultater indenfor dansk forskning i multipel sklerose. Mødet er arrangeret i samarbejde med Dansk Multipel Sklerose Center (Rigshospitalet) og er sponseret af Sclerose-foreningen samt Novartis, Sanofi, Alexion, Biogen, Merck og Roche.

14:30-15:00	**Kaffepause**
15:00-16:30	**Videnskabelig session: Basal og eksperimentel forskning (Chairs: Stephan Bramow & Yawei Liu)**
15.00-15.30	Keynote: Prof. Zsolt Illes, SDU: *"The clinical and biological continuum of MS: smouldering disease"*
15.30-15.42	Karina Juhl Damsbo, OUH/SDU; *"A FoxF2-related reparatory pathway in the brain"*
15.43-15.54	Marie Mathilde Hansen; RH: *"Circulating and Cerebrospinal Fluid Monocytes in Relapsing-Remitting Multiple Sclerosis: Implications of Anti-CD20 Therapy"*
15.55-16.06	Jonathan Krieger, SDU: *"Aging and Type I Interferons as Intersecting Variables in Regulation of Demyelinating Disease"*
16.07-16.18	Agnieszka Wlodarczyk; SDU: *"Neuroprotective Microglia: A New Hope for Novel Treatments of Demyelinating Diseases"*
16.30- 16.45	**Strække-ben pause**
16.45- 18.15	**Poster-session og forfriskning (Havegangen og Udsigt)**
19:00-21:00	**Middag inkl. uddeling af MS Forskningstalent-priserne 2024**

Lørdag 1. juni 2024

9:00-10:00	**Klinisk program – MS rehabilitering, sygepleje og symptomatisk behandling (Chairs: Caroline Tørring & Ulrik Dalgas)**
09.00-09.30	Keynote: Peter Feys, Hasselt University, Belgien *"Embracing the complexity of MS rehabilitation"*
09.31-09.42	Lars Næsby Hvid; Sclerosehospitalerne *"Effects of MS Ballroom Fitness™ on balance, walking capacity, and well-being in Multiple Sclerosis – a randomized controlled trial"*
09.43-09.54	Laurits Emil Taul Madsen, AU *"A head-to-head comparison of the effectiveness of aerobic vs. resistance training on walking endurance and fatigue in people with multiple sclerosis"*.
10:00-10:20	**Kaffepause**
10:20-11:10	**Klinisk program – MS diagnostik og epidemiologi (Chairs: Matthias Kant & Jette Frederiksen)**
10.20-10.50	Keynote: Keld Erik Byg, OUH: *"Neurosarkoidose"*
	PRÆSENTATION AF CASES
10.50-11.00	Caroline Tørring, AUH *"Svimmelhed og dobbeltsyn hos ung kvinde"*
11.00-11.10	Betul Okutan, RH *"Opticus neuritis og multiple hvid substans læsioner hos patient med fenylketonuri"*
11:10-11.25	**Kort pause**
11:25-12:10	**Klinisk program – MS behandling (Chairs: Tobias Sejbæk & Anja Thormann)**
11.25-11:55	Keynote: Zoe van Kempen, Amsterdam UMC *"Extended Interval Dosing of monoclonal antibody therapy"*
	PRÆSENTATION AF CASES
11.55-12.05	Jane Sterndorff Winkel, Kolding *"Neuroborreliose hos en patient med primær progressiv multipel sklerose under behandling med ocrelizumab"*
12.05-12.15	Stephan Bramow, RH *"Rygmarvs- og rodpåvirkning hos kvinde i 60'erne"*
12:15-13:00	**Frokost**
13:00-13:45	**DMSG møde**
13:45-14:30	**Generalforsamling DAREMUS**

Abstracts

Videnskabelige foredrag

Deeskalation af sygdomsmodificerende behandling i Danmark – et nationalt registerstudie.

FORFATTERE: Elberling, Frederik[1]; Pontieri, Luigi[1]; Mahler, Mie Reith[1]; Magyari, Melinda[1, 2]

INSTITUTION: [1] Det Danske Scleroseregister, Afdeling for Hjerne- og Nervesygdomme, Rigshospitalet – Glostrup. [2] Institut for Klinisk Medicin, Københavns Universitet.

HYPOTESE: Deeskalation fra høj-effektiv behandling (HeDMT) til moderat effektiv behandling (MeDMT) er en effektiv behandlingsstrategi i forhold til at reducere kliniske og radiologiske tegn på sygdomsaktivitet hos patienter med multipel sklerose (MS).

METODE: Kohortestudie baseret på data fra det Danske Scleroseregister inkluderende patienter med (i) attakvis MS; (ii) deeskalation siden 2006 af andre årsager end graviditet; (iii) <1 års behandlingspause mellem stop af HeDMT og start af MeDMT; (iv) ≥6 måneder på HeDMT. Vi beskriver demografiske, kliniske og behandlingsmæssige karakteristika hos deeskalerende patienter ved MeDMT-initiering (baseline). Vi præsenterer andelen af patienter, der oplever (a) attakker eller nye T2-lesioner på MR-scanning og (b) forværring af Expanded Disability Status Scale (EDSS) score efter deeskalering. Multivariabel Cox-regression anvendes for at evaluere sammenhænge mellem baseline demografiske og kliniske karakteristika med (1) tid til første attak og (2) tid til sygdomsaktivitet defineret som attak, nye T2-læsioner eller angivelse af behandlingsstop grundet sygdomsaktivitet.

RESULTATER: 333 patienter deeskalerede behandling (76% kvinder) med en gennemsnitsalder på 45.1 år ved MeDMT-initiering. De fleste deeskalerede fra natalizumab og fingolimod primært på grund af sygdomsaktivitet eller JCV-positivitet. Median opfølgningstid på MeDMT var 0.9 år.

I deeskalationsperioden oplevede 156 (46.9%) patienter enten attak eller nytilkomne MR-forandringer. Derudover havde 3 patienter (0.9%) forværring af EDSS-score, hvorimod 53.2% oplevede hverken EDSS-forværring eller sygdomsaktivitet.

Ved opfølgningsperiodens afslutning fortsatte 18.3% af patienterne med MeDMT, og hos patienter, der stoppede MeDMT, var hyppigste årsag sygdomsaktivitet (73.5%). 43.2% af patienterne reeskalerede, 20.7% skiftede til en anden MeDMT og 10.8% var uden sygdomsmodificerende behandling.

Højere alder var forbundet med en lavere risiko for både attak (hazard ratio [HR]: 0.96; 95% CI 0.94 - 0.99) og attak eller nye T2-læsioner (HR: 0.97; 95% CI 0.95 - 0.99). Registreret sygdomsaktivitet på HeDMT var forbundet med en højere risiko for attakker (HR:1.60; 1.04-2.47) og attak eller nye T2-læsioner (HR: 2.06; 1.46 - 2.91).

Risikoen for reeskalering af behandling var nedsat med 36% hos mænd og stigende alder nedsatte risikoen for reeskalation med 4% for hvert år.

DISKUSSION: I dette landsdækkende observationsstudie fandt vi, at deeskalationsstrategien kan være til gavn for ældre patienter med stabil sygdom under behandling med højeffektive præparater.

Efficacy of Progressive Power Training in Enhancing Neuromuscular and Physical Function in Older Patients with Multiple Sclerosis

FORFATTERE: Gaemelke, Tobias[1]; Feys, Peter[2]; Laustsen, Christoffer[3]; Dalgas, Ulrik[1]; Hvid, Lars[1,4]

INSTITUTION: [1] Exercise Biology, Department of Public Health, Aarhus University, Aarhus, Denmark, [2] REVAL, Rehabilitation Research Center, Faculty of rehabilitaion, Hasselt University, Hasselt, Belgium, [3] The MR Research Center, Department of Clinical Medicine, Aarhus University, Aarhus, Denmark, [4] The Danish MS Hospitals

HYPOTHESIS: Exercise has demonstrated positive effects in young and middle-aged people with multiple sclerosis (pwMS) as well as healthy older adults. However, there is a paucity of evidence investigating the effects of exercise in older (≥60 years) pwMS, despite being a growing MS subpopulation constituting one-third of the MS population. Hence, the current study aims to compare the effects of 24 weeks of progressive power training (PPT) with a usual care control group in older (≥60 years) pwMS on neuromuscular- and physical function, assessed at baseline and after 24 weeks.

METHODS: The 'Power Training in Older MS patients' (PoTOMS) randomised controlled trial included 41 older pwMS, with 21 randomised to the PPT group (65±4 years, 3.5 [2.75;4.0] EDSS) and 20 to the control group (66±4 years, 3.5 [2.63;4.5] EDSS). Participants underwent bilateral leg-press dynamometry to evaluate maximal voluntary contraction (MVC) and rate of force development at 30 ms (RFD_{30ms}), maximal chair rise, timed 25-foot walk test (T25FWT), six-minute walk test (6MWT), and 9-step stair accent (9SSA).

RESULTS: At 24 weeks, between-group difference (mean difference [95%CI]) was observed for all selected outcomes, favouring the PTT group: Maximal chair rise power (4.8 $W \cdot kg^{-1}$ [3.2;6.3], p<0.001), leg-press MVC (3.4 $N \cdot kg^{-1}$ [1.6;5.2], p<0.001), leg-press RFD_{30ms} (440 $N \cdot s^{-1}$ [8;873], p=0.046), T25FWT (0.44 $m \cdot s^{-1}$ [0.29;0.59], p<0.001) 6MWT (54 m [42;67], p<0.001), 9SSA (0.03 flight of stairs $\cdot s^{-1}$ [0.01;0.05], p<0.004). In the PPT group, clinically meaningful improvements were observed in 57% of older pwMS for the T25FWT and 60% for the 6MWT.

DISCUSSION: PPT in older pwMS was safe and effective, eliciting improvements in neuromuscular function and physical function. These improvements in physical function were clinically meaningful in a substantial proportion of older pwMS. The results highlight the effectiveness of applying PPT in this under-investigated subpopulation of older pwMS.

Follikulære T-hjælper celler ved multipel sklerose og effekten af anti-CD20 behandling

FORFATTERE: El Mahdaoui, Sahla; Hansen, Marie Mathilde; Hansen, Malene Bredahl; Hvalkof, Victoria Hyslop; Søndergaard, Helle Bach; Mahler, Mie Reith; Romme Christensen, Jeppe; Sellebjerg, Finn; von Essen, Marina Rode

INSTITUTION: Dansk Multipel Sklerose Center, Københavns Universitetshospital – Rigshospitalet, Glostrup

HYPOTESE: Follikulære T-hjælper (Tfh) celler er specialiserede i at hjælpe B-celler med modning, og interaktionen mellem gensidigt afhængige Tfh-celler og B celler antages at bidrage til patogenesen ved multipel sklerose (MS). Tfh-celler er øget i cerebrospinalvæsken (CSV) hos personer med MS, men hvorvidt anti-CD20 behandling påvirker Tfh-celler er endnu ukendt. Vores hypotese for dette studie var, at anti-CD20 behandling reducerer Tfh-celler i blod og CSV.

METODE: Vi sammenlignede frekvensen og fænotypen af cirkulerende og CSV Tfh-celler hos kontroller, behandlingsnaive- og anti-CD20 behandlede personer med attakvis multipel sklerose (RRMS) ved brug af flow cytometri. Derudover undersøgte vi sammenhængen mellem CSV Tfh-celler, kontrastopladende læsioner på MR-skanninger af hjernen og IgG index.

RESULTATER: Ubehandlede personer med RRMS har øget frekvens af Tfh-celler i CSV sammenlignet med kontroller. Ved sammenligning af blod og parret CSV var der en øget forekomst af $CD25^-$ Tfh-celler i CSV hos personer med RRMS, men ikke hos kontroller. Frekvensen af $CD25^-$ Tfh-celler i CSV korrelerede med antallet af kontrastopladende læsioner på MR-skanning af hjernen og CSV IgG index hos personer med ubehandlet RRMS. Anti-CD20 behandlede personer med RRMS havde færre cirkulerende aktiverede ($PD1^+$) Tfh-celler og $CD25^-$ Tfh-celler, og en lavere frekvens af $CD25^-$ Tfh-celler i CSV end ubehandlede personer med RRMS.

DISKUSSION: Vores studie viser, at der er en specifik intratekal rekruttering af $CD25^-$ Tfh-celler ved RRMS, samt at CSV $CD25^-$ Tfh-celler er associeret med fokal sygdomsaktivitet og intratekal B-celle aktivitet. Endelig fandt vi, at anti-CD20 behandling er forbundet med en reduktion af både cirkulerende og CSV $CD25^-$ Tfh-celler. Samlet støtter studiets fund en mulig involvering af CSV $CD25^-$ Tfh-celler ved MS, og en reduktion heraf som del af virkningsmekanismen ved anti-CD20 behandling.

Cerebrospinal fluid neurofilament light chain as a biomarker for early diagnosis of multiple sclerosis in patients with optic neuritis

FORFATTERE: Passali, Moschoula[1,2], Galea, Ian[3], Knudsen, Maria Højberg[2,4], Lau, Laurie Chi[3], Cramer, Stig Præstekjær[4], Frederiksen, Jette Lautrup[1,2]

INSTITUTION: [1]Optic Neuritis Clinic, Danish Multiple Sclerosis Center, Department of Neurology, Copenhagen University Hospital Rigshospitalet-Glostrup, Denmark, [2]Department of Clinical Medicine, Faculty of Health and Medical Science, University of Copenhagen, Denmark, [3]Clinical Neurosciences, Clinical and Experimental Sciences, Faculty of Medicine, University of Southampton, Southampton UK, [4]Functional Imaging Unit, Department of Clinical Physiology, Nuclear Medicine and PET, Copenhagen University Hospital Rigshospitalet-Glostrup, Denmark

HYPOTHESIS: Early diagnosis of multiple sclerosis (MS) allows for early treatment initiation which is related to lower long-term disability. In this study, we explored whether incorporation of CSF neurofilament light chain (cNfL) into the 2017 McDonald criteria would accelerate diagnosis of MS in patients with optic neuritis (ON). Furthermore, we investigated the relationship between cNfL, dissemination in time (DIT), oligoclonal bands (OCB) and dissemination in space (DIS).

METHODS: cNfL was measured (ELISA, UmanDiagnostics) in diagnostic samples from patients with verified ON participating in a clinical trial (NCT03451955). MS was diagnosed using the 2017 McDonald criteria at the time of recruitment (early MS-converters) or within a minimal follow-up time of two years (later MS-converters).

RESULTS: cNfL was measured in 74 ON patients. The 2017 McDonald criteria allowed for early diagnosis at the time of ON debut in 79.6% of MS-converters. Both early MS-converters (1390 [903, 1850], p=0.0077) and later MS-converters (1590 [1300, 1820], p=0.009) had increased cNfL compared to non-converters (676 [352, 1290]). Presence of OCB was associated with 107% (48%-190%) higher cNfL ($p=4.8x10^{-5}$, adjusted for age). Similarly, presence of MRI lesions typical of MS in one CNS cite was associated with 107% (33%-223%, adjusted for age, p=0.0016) higher cNfL levels. Demonstration of additional MRI criteria for DIS was not associated with further increases in cNfL. In a univariate logistic regression model, a doubling of cNfL was associated with 190% (69%-460%, p=0.00043) higher odds of MS and an area under the curve (AUC) of 0.748. Adding cNfL to a multivariate logistic regression model with MRI criteria for DIS (<2 or ≥2) and OCB as independent variables resulted in an increase of the AUC from 0.955 to 0.970. Incorporation of cNfL as a substitution for either 1 criterion for DIS or OCB allowed for earlier diagnosis of 55.6% of later MS-converters but misclassified 6.7% of non-converters.

DISCUSSION: Measurements of cNfL could accelerate the diagnosis of MS in a subset of patients with ON. Performance of larger multicenter studies is encouraged to improve sensitivity and specificity estimates depending on whether cNfL is used as a substitution of DIT, DIS or both.

Hvordan påvirker anti-CD20-behandling immuncellerne i blodet hos multiple sklerose-patienter?

FORFATTERE: Wæde, Mie[1,2,3], Voss, Lasse F.[4], Kingo, Christina[1,2,3], Thomassen, Mads[5,2], Gjerstorff, Morten[3], Møller, Jesper B.[3], Elkjær, Maria L.* [1,2,3], og Illes, Zsolt* [1,2,3].

**Lige bidrag*

INSTITUTION: [1]Neurologisk Afdeling, Odense Universitets Hospital. [2]Klinisk Institut, Syddansk Universitet. [3]Institut for Molekylær Medicin, Syddansk Universitet. [4]Institut for Sundhedsteknologi, Danmarks Tekniske Universitet. [5]Klinisk Genom Center, Odense Universitets Hospital.

HYPOTESE: Det er stadig uklart, hvordan anti-CD20-behandling påvirker andre immunceller, der ikke udtrykker CD20. Vi tror, at en undersøgelse af CD20-negative immunceller vil hjælpe os med at forstå anti-CD20-behandlingens virkningsmekanismer i MS-patienter og muliggøre identifikationen af potentielle biomarkører for MS.

METODE: Vi har isoleret PBMC (mononukleare immunceller i blodet) fra MS-patienter før og under deres anti-CD20-behandling på 3 forskellige tidspunkter; akut B-celle-fjernelse (21 dage efter behandlingsstart), immungendannelse (lige før anden behandlingscyklus) og komplet B-celle-fjernelse (2 måneder efter anden behandlingscyklus). Vi har udført spektral flerfarvet flow-cytometri (19 antistoffer mod overflademarkører) og single-celle RNA-sekventering (399 gener kombineret med 30 overflademarkører) til at undersøge de cellulære, molekylære og funktionelle ændringer i PBMC, der opstår i løbet af behandlingen. Yderligere har vi inkluderet alders- og kønsmatchet raske kontroller for at sammenligne sammensætningen af immunceller med MS-patienter fra før de startede i behandlingen.

RESULTATER: Ud fra 70 blodprøver observerer vi et akut fald i andelen af $CD56^+$ celler, NK-celler ($p<0.05$) og NK T-celler ($p<0.01$), der genoprettes før anden behandlingscyklus. Ved en nærmere undersøgelse af $CD56^+$ NK- og $CD8^+$ T-celle subpopulationer ser vi klare fænotypiske ændringer. Et signifikant fald af $CD56^+$ celler positive for chemokin-receptorerne, CXCR3 og CCR7, observeres under anti-CD20-behandling ($p<0.01$), og samtidig observeres en øgning af $iKIR^+$ $CD56^+$ celler under behandlingen ($p<0.05$). Antallet af $PD\text{-}1^+$ $CD8^+$ T-celler falder drastisk under anti-CD20-behandlingen ($p<0.001$), og samtidig observeres en gradvis stigning i $CD8^+$ Treg-celler ($p<0.01$) under behandlingen.

DISKUSSION: $CD56^+$ NK- og $CD8^+$ T-celler har cytotoxicisk aktivitet, der kan påvirke MS-patogenesen. $CXCR3^+CCR7^+$ NK-celler anses for at være CNS-infiltrerende, hvor andelen af disse falder under anti-CD20-behandlingen, mens $iKIR^+$ NK-celler med en mere kontrolleret fænotype stiger. Fjernelsen af B-celler leder også til et fald af udmattede $PD\text{-}1^+$ $CD8^+$ T-celler og en stigning i $CD8^+$ Treg-celler. Disse resultater indikerer, at anti-CD20-behandling medfører en funktionel og fænotypisk ændring i subpopulationer af cytotoxiske immunceller fra en aktiv, pro-inflammatorisk tilstand til en mere kontrolleret og regulatorisk fænotype. Dette betyder, at anti-CD20-behandling ikke kun har en direkte effekt på $CD20^+$ B-celler og $CD20^{dim}$ T-celler, men også en indirekte effekt på $CD20^-$ celler.

Barriers to Clinical follow-up visits in multiple sclerosis: A Nationwide register-based study

FORFATTERE: Beczek, Agata[1,7]; Landt, Eskild Morten [2]; Storr, Lars Kristian [1]; Beck, Malene [3,4,5]; Magyari, Melinda[6]; Dahl, Morten [2,7]

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BACKGROUND: Treatment of people with Multiple Sclerosis (PwMS) is mainly provided by specialized Multiple Sclerosis (MS) clinics and focuses on recovery from attacks, preventing relapses, slowing diseases progression and managing symptoms. However, not all PwMS are followed in MS clinics. Studies often relies on participants who are clinic-based, and the research on PwMS who do not attend regular clinical follow-up is limited.

OBJECTIVE: To identify the prevalence of PwMS with low attendance in Danish MS clinics and identify barriers of this.

METHODS: This nationwide register-based cohort study includes individuals with a confirmed MS diagnosis in Denmark during the period 2000-2020. Danish Multiple Sclerosis Registry and Statistics Denmark are the main sources of the study dataset. To examine associations we used bivariate analysis and logistic regression, comparing PwMS with less than 1 annual clinical follow-up visit, to control subjects with 1 or more annual clinical follow-up visit.

RESULTS: We included 10,173 adults with MS, out of which 3,860 (38 %) had less than one clinical follow-up visit annually, categorizing them as having low-attendance. The comparison between patients with low attendance and control subjects revealed significant differences: age at diagnosis was higher for the low-attendance group (43 years) compared to the control group (37 years), with a statistically significant difference $p<0.001$. A higher percentage of patients in the low-attendance group had primary-progressive MS (25% vs 3%, $p<0.001$) and higher proportion of Expanded Disability Scale scores ≥4.5 (37% vs 22%, $p<0.001$). The odds of less than 1 clinical follow-up visit occurring increased by: never received disease modifying treatment (OR=25.36, 95%CI: 18.46 – 34.85); diagnosis in year 2000-2009 (OR=2.35, 95%CI: 2.14 – 2.58); affiliated to an MS clinic in an outer region (OR=2.32, 95%CI: 2.08 – 2.60); progressive MS type (OR=1.72, 95%CI: 1.52 – 1.96) and being 40 years or older at diagnosis (OR=1.64, 95%CI: 1.49 – 1.81).

DISCUSSION: Our results shows geographic and disease specific inequality in the treatment of PwMS in Denmark. Strategies to prevent this inequality for people with progressive types and those who need supportive and non-medical treatment and care should be implemented.

Bad sleep = bad life? Sleep quality is clearly associated with quality of life in persons with MS – The Danish MS Hospitals Rehabilitation Study.

FORFATTERE: Langeskov-Christensen, Martin[1,2]; Boesen, Finn[3]; Trénel, Philipp[3]; Kirov, Filip[1]; Skjerbæk Anders G.[3,4]; Hvid, Lars G.[3,4]

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HYPOTHESIS: Sleep disturbances are prevalent among persons with MS (PwMS). Whilst the relationship between sleep quality and health-related quality of life (HRQoL) in PwMS is currently underexplored, such knowledge seems crucial to optimize rehabilitation / management strategies targeting sleep in PwMS. We aimed to examine associations between sleep quality and HRQoL in PwMS, hypothesizing that these associations would be strong.

METHODS: This was a secondary analysis of the Danish MS Hospitals Rehabilitation Study. PwMS aged 18- 65 years and with an expanded disability status scale (EDSS) score ≤7.5 participated. Baseline data comprised patient- and disease-related characteristics, sleep quality (Pittsburgh Sleep Quality Index (PSQI)), and MS-specific health-related quality of life (HRQoL; Functional Assessment of MS questionnaire (FAMS)). Simple and multiple (adjusting for age, sex, EDSS) regression analyses were used to examine associations between sleep quality and HRQoL. A linear mixed model was used to compare FAMS scores across sleep quality subgroups (i.e., "good sleepers" = PSQI 0-5, "poor sleepers" = PSQI 6-10, "very poor sleepers" = PSQI 11-21).

RESULTS: In the sample of 405 PwMS (50±9 years, 69% females, EDSS 4.8±1.5) total PSQI was 6.5±3.6 (55% were categorised as "poor" or "very poor" sleepers). Sleep quality was significantly associated with HRQoL in the simple (r=0.35, slope: -2.5 [-3.1;-1.8], p<0.001) as well as the multiple regression analysis (r=0.36, slope: -2.5 [-3.2;-1.9], p<0.001; minor influence from age, sex, and EDSS). Correspondingly, lower FAMS scores were observed in "poor sleepers" (-10.3 [-15.5;-5.2]) and "very poor sleepers" (-20.0 [-26.7;-13.3]) compared to "good sleepers". Also, "very poor sleepers" scored lower (-9.7 [-16.6;-2.8]) compared to "poor sleepers". These group differences exceeded what is deemed a minimal clinically important difference (3 point).

DISCUSSION: The present findings stress the vital role of addressing sleep quality, an 'invisible' symptom, in the rehabilitation of PwMS, as it was significantly associated with HRQoL. Improving sleep quality may substantially improve HRQoL in PwMS.

Increased blood-brain barrier permeability in optic neuritis patients with early diagnosis of multiple sclerosis.

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HYPOTHESIS: We explored the relationship between blood-brain barrier (BBB) permeability in normal-appearing white matter (NAWM) and MS-related biomarkers in optic neuritis (ON). Furthermore, we tested whether measurements of BBB permeability in NAWM could predict the diagnosis of MS in our cohort of ON.

METHODS: BBB permeability – defined as the influx constant K_i from Patlak models – was measured in the NAWM of patients with verified ON using dynamic contrast-enhanced MRI (DCE-MRI). MS was diagnosed using the 2017 McDonald criteria with a minimal follow-up time of 2 years. Data on dissemination in time and space, cerebral contrast enhancing (CE) lesions, visual acuity, Velhagen pseudoisochromatic color vision test, retinal nerve fiber layer thickness, oligoclonal bands, CSF leukocyte concentration, IgG-index, vitamin D and Qalb (CSF albumin/ plasma albumin) were obtained. Differences between groups were evaluated using Mann–Whitney U test and linear regression. Univariate logistic regression and receiver operating characteristic curves were used to evaluate whether Ki could predict MS.

RESULTS: DCE-MRI was performed among 78 ON patients (49 MS-converters and 29 non-converters). MS-converters had higher K_i compared to non-converters (p=0.026). Logistic regression analysis showed a trend for Ki predicting conversion of ON to MS (p=0.068). Ki was highest in patients fulfilling the 2017 McDonald criteria for MS already at ON debut and these early MS-converters had 60.8% (6.2%-143.5%, p=0.026) higher Ki compared to non-converters. We found a positive correlation between K_i and the number of fulfilled MRI criteria for dissemination in space (Spearman's □=0.3, p=0.0074). ON patients with cerebral CE lesions had higher K_i compared to ON patients without cerebral CE-lesions (p=0.04). Similarly, a trend was observed when comparing ON patients with and without oligoclonal bands (p=0.067). We found no correlation between K_i and other investigated biomarkers.

DISCUSSION: We detected subtle increases of BBB permeability in the NAWM of patients fulfilling the 2017 McDonald criteria of MS already at ON debut. Its correlation with the number of fulfilled MRI criteria for dissemination in space could suggest that K_i reflects a state associated with lesion formation or that Ki increases with longer disease duration.

Epidemiologisk indsigt i dansk multipel sklerose (1950-2024): Gennemsnitsalder, kønsfordeling, incidens og prævalens

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HYPOTESE: Stigende levealder i baggrundsbefolkningen og fremskridt inden for behandling af multipel sklerose (MS) burde medføre aldring af MS-populationen. Alligevel er evidensen for denne hypotese stadig sparsom. Vores studie havde til formål at afgøre om gennemsnitsalderen af den danske MS-population er steget samt analysere udviklingen i incidens, prævalens og kønsfordeling, som alle påvirker gennemsnitsalderen.

METODE: Vi gennemførte et kohortestudie ved at koble data fra Det Danske Scleroseregister med Det Centrale Personregister, Dødsårsagsregisteret og Migrationsregisteret. Vi inkluderede alle levende patienter med en bekræftet MS-diagnose, der boede i Danmark den 1. januar hvert år fra 1950 til 2023. Vi beregnede gennemsnits- og medianalder, aldersfordeling, kønsfordeling, incidens og prævalens af den danske MS-population årligt fra 1950 til 2023.

RESULTATER: Vi inkluderede 28.145 personer med MS. Den gennemsnitlige alder af den danske MS-population steg frem til slutningen af 1970'erne og nåede et niveau omkring 52,5 år, hvor den stabiliserede sig indtil 1990. Derefter faldt gennemsnitsalderen gradvist til 51,2 år i 2005, efterfulgt af en stigning til sit højdepunkt på 54,2 år i 2023.

I 1975 udgjorde kvinder 58,7% af MS-populationen. Andelen steg til 65,7% i 2000 og 68,5% i 2023. Incidensen forblev stabil omkring 3,5/100.000 indtil 1975, hvorefter den gradvist steg til 11,4/100.000 i 2000. I den sidste del af observationsperioden fra år 2000 til 2022 forblev kurven relativt stabil til trods for mindre fluktuationer, men incidensen lå på sit laveste i 2022 sammenlignet med de foregående to årtier. Både den generelle og kønsspecifikke prævalens viste en opadgående tendens i hele perioden, især blandt kvinder.

DISKUSSION: Vores studie viser, at gennemsnitsalderen af den danske MS-population er steget, dog ikke så entydigt som forventet. Andelen af kvinder er vokset og det samme er prævalensen, imens incidensen muligvis har stabiliseret sig i de seneste årtier efter en periode med stigning. Vores resultater bygger på data af meget høj kvalitet, hvorfor de kan bruges som et referencepunkt for fremtidige undersøgelser.

Neurofilament light chain og glial fibrillary acidic protein er associeret med nye og/eller forstørrede T2 læsioner og hjerneatrofi

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HYPOTESE: Dimethyl fumrate er en udbredt første linje behandling som har vist en signifikant reduktion af nye T2 læsioner og neurofilament light chain (NfL). Forståelsen imellem niveauer af NfL, glial fibrillary acidic protein (GFAP) og MR-aktivitet samt hjerneatrofi kan bidrage til bedre at identificere sygdoms udvikling ved multipel sklerose (MS).

METODE: Studiet inkluderede 42 nydiagnosticere og tidligere behandlingsnaive patienter med attakvis MS. Plasma NfL og GFAP blev målt med SiMoA ved baseline, måned 6, 12 og 24. MR-scanninger af cerebrum fra baseline og frem til år 4 blev udført efter klinisk protokol og blev analyseret med icobrain (icometrix™). Årlig hjerneatrofi og læsions volumen blev kvantificeret. Association imellem blodbiomarkører og MR resultater blev analyseret med generaliseret linear model inkluderende alder som en co-variat.

RESULTATER: Studiet fandt association imellem NfL, GFAP og hjerne atrofi samt nytilkomne T2 læsioner. Niveauer af NfL ved måned 6 var associeret med nye og eller forstørrede T2 læsioner ved år 2 og 3. NfL ved måned 12 var prædiktivt for hjerneatrofi ved år 1 og 4. GFAP ved måned 6 og 12 var associeret med ny og eller forstørrede læsioner ved år 1, 2 og 3 samt hjerneatrofi ved år 1 og 3.

KONKLUSION: Plasma NfL- og GFAP-niveauer ved måned 6 og 12 var associeret med efterfølgende MR aktivitet og hjerne atrofi. Resultaterne indikerer at NfL og GFAP kunne være supplerende biomarkører i monitoreringen af MS.

A FoxF2-related reparatory pathway in the brain

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HYPOTHESIS: Comparing activated genes in brain lesions with remyelination ***vs*** ongoing damage in progressive MS (PMS) will identify molecules and pathways that contribute to repair.

METHODS: First, we examined activation of genes by next-generation RNA-sequencing (RNA-seq) in 73 brain tissues from patients with PMS (n=73) and controls (n=25). PMS tissues covered different types of lesions including chronic active expanding lesions (CL) and remyelinating lesions (RL). We compared differentially activated genes/ pathways among lesion types. Next, we induced absence of FoxF2 in all mice brain cells by injection of tamoxifen (global knock-out, KO) and in a separate model, selectively in astrocytes (astrocyte-specific KO). We then examined the effect of the induced absence of FoxF2 on experimental demyelination (DEM) and remyelination (REM) in the corpus callosum (CC) in the cuprizone (CPZ) model.

RESULTS: In PMS remyelinating lesions, we found a significant upregulation of the transcription factor FoxF2 and the cytokine receptor TGFbR2, a major hub in the remyelinating network. FoxF2 and TGFbR2 expression was related to a subset of astrocytes in RL. These data suggested a FoxF2- and TGFbR2-related reparatory pathway linked to astrocytes.
In the mouse brain, FoxF2 levels significantly decreased during DEM and increased during REM. In the global FoxF2-KO mice, MOG upregulation was deficient during REM. TGFbR2 expression increased in the CC during REM, but not in the KO mice. Proinflammatory genes TNF-alpha and IL-1 were upregulated during both DEM and REM in the FoxF2 KO mice, indicating exacerbated inflammation and deficient brain repair without FoxF2. RNA-seq of CC and astrocytes during DEM and REM in FoxF2-KO mice ***vs*** controls, revealed altered repair gene expression patterns, and inflammation-related genes were enriched during DEM. In the astrocyte-specific KO, TGFbR2 and TGFb2 expression was unchanged during DEM in contrast to their upregulation in WT astrocytes.

DISCUSSION: Our analyses of the PMS brain lesions and specific mouse model experiments indicate the reparatory role of FoxF2 and TGFbR2. Ongoing examination of FoxF2 target genes and their human orthologues in the MS brain lesions aims to identify novel molecules related to lesion repair and as potential novel treatment strategies in progressive MS.

Circulating and Cerebrospinal Fluid Monocytes in Relapsing-Remitting Multiple Sclerosis: Implications of Anti-CD20 Therapy

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HYPOTHESIS: This study investigates the implications of anti-CD20 treatment on circulating and cerebrospinal fluid (CSF) monocytes in patients with relapsing-remitting multiple sclerosis (RRMS). Previous findings from murine models and in vitro studies suggest that proinflammatory monocytes may be activated during anti-CD20 treatment due to disrupted interactions between monocytes and regulatory B cells. Our aim was to investigate whether similar effects occur in human monocytes.

METHODS: We collected CSF and/or peripheral blood from untreated (n=50) and anti-CD20-treated (n=40) patients with RRMS, and controls (n=35); symptomatic or non-inflammatory neurological disease controls. We assessed the prevalence and phenotype of monocyte subsets by flow cytometry. CSF concentrations of chitinase 1 (CHIT-1) and interleukin (IL)-10, IL-12p40, IL 15, tumor necrosis factor (TNF)-α and lymphotoxin (LT)-α were measured by immunoassays. Monocyte cytokine production after lipopolysaccharide stimulation was evaluated in untreated (n=12) and anti-CD20 treated (n=12) patients with RRMS.

RESULTS: In CSF, the monocyte phenotype was altered with higher CD16 expression, most pronounced in controls who had a 2-fold higher frequency of $CD16^+$ monocytes compared to untreated patients. After LPS stimulation a comparable proportion of monocytes from untreated and anti-CD20 treated patients produced IL-10, IL-12p40, LT-α and TNF-α. In CSF, untreated patients had higher levels of IL-10, IL-12p40, and TNF-α compared to controls, while levels in anti-CD20 treated were comparable to controls. CHIT-1 concentrations were increased in untreated patients, and despite decrease in anti-CD20 treated patients, it remained higher than in controls.

DISCUSSION: In line with previous findings, our study confirmed a CSF monocyte phenotype characterized by increased CD16 expression, particularly pronounced in controls. CSF $CD16^+$ monocytes are suggested to be involved in immune surveillance. Anti-CD20 treated patients tended to have higher frequencies of CSF CD16+ monocytes compared to untreated. Contrary to previously ***in vitro*** studies, we found no evidence of increased cytokine production by monocytes from anti-CD20 treated patients. Notably, anti-CD20 treatment led to decrease in CSF cytokine levels of IL-10 and IL-12p40, while CHIT-1 remained increased, suggesting unresolved inflammation not targeted by anti-CD20 treatment. In conclusion, our study found no evidence supporting the induction of monocyte activity by anti-CD20 treatment.

Aging and Type I Interferons as Intersecting Variables in Regulation of Demyelinating Disease

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INSTITUTION: University of Southern Denmark (SDU)

HYPOTHESIS: Multiple Sclerosis (MS) is a chronic demyelinating disease that typically manifests between the ages of 20 and 40 with a relapsing-remitting clinical course. Primary and secondary progressive MS are clinical subtypes characterized by gradual accumulation of disability without periods of remission and have a later age of onset, generally between the ages of 40 and 60, suggesting an age-related neurodegenerative process. Age-related increases in type I IFN signaling have been shown to negatively affect brain function and promote an unrestrained microglial phenotype. This study has investigated whether type I IFN-signaling influences demyelinating pathology as well as remyelination and microglial activity in middle-aged mice (10-14 months).

METHODS: MS-like pathology was induced by feeding mice cuprizone (CPZ) and the effect of type I IFN signaling was examined by comparing IFNAR1-KO with wildtype (WT) mice. Demyelination of the corpus callosum was assessed using luxol fast blue and myelin basic protein staining. Microglia were visualized using ionized calcium-binding adaptor molecule 1 (Iba1) staining. We also assessed weight fluctuation of aged mice fed with 0,3% CPZ pellets as a measure of tolerability and treatment-success. As an alternative approach, we will induce a focal laser-induced injury using a two-photon laser to induce a focal burn injury in the cortex.

RESULTS: Results indicate that aged IFNAR1-deficient mice display a greater tolerance towards cuprizone treatment and may demyelinate at a slower rate than their WT counterparts. Data suggest that IFNAR1-deficiency may impair the phagocytosis of myelin by microglia. Effect of age and IFNAR1 deficiency on remyelination is currently being studied. Further histological analysis of brains from this study will extend understanding of age and Type I IFN-related differences in pathology.

DISCUSSION: These data describe a novel examination of the impact of type I IFN signaling on demyelinating pathology in the aged brain environment. Additional mouse brains from this study will be used to repeat histological analysis with the aim of achieving statistical significance regarding differences in pathology. Important findings from this study that necessitate further investigation involve determining whether IFNAR1-deficiency causes a significant delay in demyelination, whether this delay corresponds with reduced microglial myelin phagocytosis, and exploring potential connections with IFNAR1-dependent disruptions in remyelination.

Neuroprotective Microglia: A New Hope for Novel Treatments of Demyelinating Diseases.

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BACKGROUND: Microglia, the resident macrophages of the central nervous system (CNS), play a crucial role in maintaining brain health through immune surveillance and rapid response to tissue injury. Despite their protective potential in conditions like multiple sclerosis (MS) through debris clearance and cytokine release, adult microglia often fall short in supporting full recovery. Our research has led to the identification of a novel subpopulation of microglia found in the neonatal brain, distinguished by its expression of neurogenic, myelinogenic, and angiogenic factors critical for neurodevelopment and repair, a feature absent in adult microglia.

HYPOTHESIS: Leveraging this discovery, we propose that transplanting neuro-supportive neonatal microglia into animal MS models might enhance, or even restore, functional capacity.

METHODS: To examine this hypothesis, microglia were isolated from mice aged 3-5 days and transplanted into adult animals exhibiting MS-like symptoms, specifically those with experimental autoimmune encephalomyelitis (EAE) and Cuprizone-induced demyelination. The assessment focused on functional recovery and remyelination post-transplantation.

RESULTS: Our findings demonstrate that neonatal microglia transplanted into the cerebrospinal fluid of adult mice with symptomatic EAE migrate towards and accumulate at spinal cord inflammatory lesions. This migration significantly alleviates EAE symptoms and is accompanied by reduced immune infiltration and the induction of remyelination. Similar remyelinating effects were observed in the context of Cuprizone-induced demyelination.

DISCUSSION: The identified neonatal microglial phenotype showcases potent re-myelinating and anti-inflammatory capabilities. Further elucidating the mechanisms underlying these protective effects could pave the way for novel therapies targeting neuroinflammatory diseases. This research not only highlights the therapeutic potential of neonatal microglia in treating MS but also emphasizes the importance of understanding microglial diversity and plasticity in designing new treatment strategies.

Effects of MS Ballroom Fitness™ on balance, walking capacity, and well-being in Multiple Sclerosis – a randomized controlled trial

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HYPOTHESIS: Multiple sclerosis (MS) is accompanied by balance and walking dysfunction alongside deterioration of mental well-being and health-related quality of life (QoL). MS Ballroom Fitness™ (MS_{B-Fit}) is a personalized dance/fitness-based concept targeting exactly these challenges. However, few studies involving persons with MS (pwMS) have investigated the effects of MS_{B-Fit} (or other dance/fitness-based interventions). We aimed to explore this by using a cluster randomized controlled study design. Our hypothesis was that MS_{B-Fit} would elicit numerous health benefits including improvements in balance, walking, mental well-being, and QoL.

METHODS: A total of n=91 ambulatory pwMS were enrolled (93% females, 54±9 years, patient determined disease steps 2.6±1.5 [range 0-7]) and evenly randomized into intervention (MS_{B-Fit}: n=44, group-based, 2 sessions/week, 50-60 minutes/session, mix of dance and fitness, moderate-to-high intensity or complexity) or control (CTRL; n=47, continuation of habitual living). Outcomes included the six spot step test (SSST; walking coordination- and balance; ***primary outcome***), the four square step test (FSST; dynamic balance and coordination), the 6-minute walk test (6MWT; walking endurance), the VAS 0-100 health-related quality of life (HR-QoL), and the WHO-5 mental well-being index (WHO5).

RESULTS: Between-group improvements (mean [95%CI]) in favor of MS_{B-Fit} were observed for SSST (0.008 [0.003;0.013] testruns/s, p<0.01; ***corresponds to a reduction of -0.77 seconds***), FSST (0.018 [0.010;0.027] testruns/s, p<0.01; ***corresponds to a reduction of -1.04 seconds***), 6MWT (36 [19;52] m, p<0.01), HR-QoL (7.7 [2.7;12.8] points, p<0.05), and WHO5 (7.4 [1.4;13.4] points, p<0.05). This was achieved by improvements in MS_{B-Fit}, whereas CTRL remained unchanged.

DISCUSSION: The present study showed that MS Ballroom Fitness™ (MS_{B-Fit}) is a very effective exercise modality in improving balance and walking capacity alongside mental well-being and QoL in pwMS. The next step is to explore how MS_{B-Fit} can be implemented throughout Denmark.

A head-to-head comparison of the effectiveness of aerobic vs. resistance training on walking endurance and fatigue in people with multiple sclerosis.

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HYPOTHESIS: Walking impairments and fatigue are two common symptoms in people with multiple sclerosis (PWMS), both known to be positively affected by aerobic training (AT) and resistance training (RT). However, the effects of the two modalities have not been directly compared. We hypothesized that both modalities would improve walking and fatigue as compared to usual care (control).

METHODS: A total of n=150 pwMS (45 ± 8 years, 74 % women) were enrolled and randomized into either 12 weeks of AT (n=60, 30 sessions), RT (n=60, 30 sessions), or control ('usual care', n=30). Evaluation of, among others, isometric knee extensor muscle strength (MVC; isokinetic dynamometry), aerobic capacity (VO2peak; incremental exercise test), fatigue (Modified Fatigue Impact Scale), and six-minute walk test (6MWT) were evaluated before and after.

RESULTS: Aerobic capacity increased in AT vs. control by 4.3 [1.5;7.1] mL o_2/min/kg (***mean [95CI]***) and in AT vs. RT by 3.2 [0.9;5.5], but not in RT vs. control (1.1 [-1.6;3.9]). Knee extensor muscle strength increased in RT vs. control by 0.87 [0.04;1.7] Nm/Kg and in RT vs. AT 0.75 [0.27;1.21], but not in AT vs. control (0.14 [-0.18;0.47]). 6MWT increased in RT vs. control by 26 [2; 50] m and in RT vs. AT 18 [-2;38] (trend), but not in AT vs. control (8 [-15; 32] m). $MFIS_{total}$ seemed not to be reduced in neither RT vs. control -5.6 [-14.9; 3.7] points nor in AT vs. RT -2.6 [-9.1; 3.9], although a trend was observed in AT vs. control -8.2 [-17.5; 1.1]. $MFIS_{physical}$ seemed not to be reduced in AT vs RT -0.59 [-3.7; 2.5], whereas a trend towards a reduction was observed in RT vs. control -4.3 [-8.8; 0.2] points alongside a reduction in AT vs. control -4.9 [-0.4;-9,4]. $MFIS_{cognitive}$ remained unaffected in all groups.

DISCUSSION: RT and AT elicited improvements in physiological factors. 6MWT was increased in RT only and no apparent differences were observed between the effects of AT and RT on fatigue. However, both modalities (AT in particular) seemed superior to control in eliciting reductions in $MFIS_{physical}$. RT seem superior in improving walking endurance and AT in reducing physical fatigue.

NOTER

Abstracts

Videnskabelige posters

Evaluation of the effect of CD-20 depleting therapy on virus antibody levels in multiple sclerosis patients

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HYPOTHESIS: Multiple sclerosis (MS) is a chronic demyelinating disease of the central nervous system. Evidence indicates that Epstein-Barr virus (EBV) is involved in the development of the disease, which is in accordance with that antibodies to Epstein-Barr nuclear antigen 1 (EBNA1) are elevated in patients with MS. In this study we evaluated the effect of CD-20-depleting therapy on various virus antibodies to determine whether virus antibodies may function as diagnostic markers and in treatment monitoring.

METHODS: Specific IgG concentrations against 10 common viruses such as EBV, measles virus (MeV) and mumps virus (MeV), rubella virus (RuV), cytomegalovirus (CMV), influenza virus A (IVA), varizella zoster virus (VZV) and human herpes virus 6 (HHV6) were examined in from relapsing-remitting (RR)MS patients (n=27) and healthy controls (n=15) (HCs) serum by direct enzyme-linked immunosorbent assays. In total, 27 RRMS patients donated 42 blood samples, 13 samples were collected at baseline prior to CD-20-depleting ocrelizumab therapy, whereas 29 serum samples were collected during routine follow-up. RRMS patients (F:M 16:10, 41.94 years) and HCs (F:M 10:5, 42.15 years) were sex- and age matched when possible.

RESULTS: A trend indicated elevated EBV IgG levels in MS patients compared to HCs independent of CD20-depleting therapy. This observation only related to the latent state Epstein-Barr nuclear antigen 1 (EBNA1) and not the lytic state-expressed BamHI-A rightward frame 1 (BARF1) protein. Also, elevated IgG levels to MeV nucleoprotein were detected in serum samples from RRMS patients at baseline. In general, virus IgG titers were not influenced by CD-20-depleting therapy and the effect of ocrelizumab treatment on virus antibody levels varied from patient to patient.

DISCUSSION: The current findings support that elevated virus antibody levels primarily associate to EBV EBNA1, supporting that EBV EBNA1 IgG may supplement early MS diagnostics, whereas the application of virus antibodies in disease and treatment monitoring is limited.

Sleep disorders and sleep disturbances in persons with multiple sclerosis

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HYPOTHESIS: Adverse sleep is common in multiple sclerosis (MS). There is a lack of population-based studies including adequate control groups. The prevalence of sleep disorders and other sleep disturbances was hypothesized to be higher in persons with MS than in controls without MS.

METHODS: We conducted a population-based matched case-control study linking individual-level data from the Danish MS Registry (n=21,943 persons with MS) and the Danish Population Registry (n=109,715 matched controls) with information on sleep disorders from the Danish National Patient Registry and other sleep disturbances assessed by dispensed prescription medication from the Danish National Prescription Registry.

RESULTS: Prevalence of diagnosed sleep disorders in terms of central hypersomnia (0.15% (persons with MS) vs. 0.06% (controls)), sleep disturbances (1.05% vs. 0.70%), and sleep movements (0.22% vs. 0.13%) and other sleep disturbances identified by dispensed central acting (10.73% vs. 1.10%) and hypnotic use (30.65% vs. 20.13%) medication was statistically significantly higher among persons with MS when compared to matched controls. There was no statistically significant difference in the prevalence of sleep apnea and parasomnia between the two groups. Stratified for sex, results for differences between persons with MS and controls were similar.

DISCUSSION: In this registry-based study, we found that the prevalence of several sleep disorders was higher in persons with MS than in matched controls, that is those reflecting insomnia and daytime symptoms including hypersomnia. Other sleep disturbances identified by dispensed prescription medication was markedly higher in persons with MS than matched controls.

Real-World Study: Impact of Alemtuzumab on Fatigue, Quality of Life, and Patient/Caregiver Reported Outcomes in relapsing-remitting Multiple Sclerosis

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HYPOTHESIS: Alemtuzumab is approved for treatment of highly active relapsing–remitting multiple sclerosis (RRMS) in the European Union. We hypothesize that patient reported outcomes (PROs) document information on the patients' disease state and assess the impact of alemtuzumab on their quality of life (QoL). Understanding the caregiver reported outcomes (CROs) in a real-life treatment setting is essential for MS treatment.

METHODS: This 36-month, real-world, observational study enrolled 87 RRMS patients undergoing alemtuzumab treatment in three European countries. The primary endpoint was the effect on MS-related fatigue (Fatigue Scale for Motor and Cognitive Functions [FSMC]). Secondary endpoints included effect on cognition (Symbol Digit Modality Test [SDMT]), depression (Beck Depression Inventory–Version II [BDI-II]), QoL (Multiple Sclerosis Impact Scale-29 item [MSIS-29]), treatment satisfaction, number of relapses, improvement in Expanded Disability Status Scale (EDSS) score, and safety. Exploratory endpoints included CROs.

RESULTS: Of 87 enrolled patients, 72.4% (n=63) completed six follow-up visits. Statistically significant improvements were found for FSMC ($p<0.01$), SDMT ($p<0.05$), depression ($p<0.01$) and QoL scores (MSIS-29, physical ($p<0.01$) and psychological ($p<0.001$)). Global treatment satisfaction ($p<0.001$), effectiveness ($p<0.05$) and side effects ($p<0.05$; apart from at EOS) also showed significant improvements at all time points. The percentage of patients with at least one relapse remained consistent throughout the study (10.8%–13.2%). EDSS improved significantly ($p<0.05$). Caregivers reported an increase in emotional QoL. One treatment-related death occurred, and no new safety concerns were reported.

CONCLUSION: This real-world study demonstrated beneficial impact of alemtuzumab on fatigue, cognition, depression, QoL and treatment satisfaction. Moreover, disability improvement over time was reported.

Identification of cut-points for walking capacity in patients with Multiple sclerosis

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HYPOTHESIS: Walking capacity is substantially impaired in patients with Multiple sclerosis (PwMS). Assessment and interpretation of walking capacity are thus important to both patients, in clinical practice, and research. However, little research has been done to establish clinically relevant cut-points for commonly used tests of walking capacity in PwMS such as the 6-Minute Walk Test (6MWT), Six Spot Step Test (SSST), and Timed 25-Foot Walk Test (T25FWT). We hypothesised that clinically relevant cut-points can be identified for the 6MWT, SSST, and T25FWT in relation to patient-reported walking ability measured by the 12-item Multiple Sclerosis Walking Scale (MSWS-12) in PwMS.

METHODS: A total of 211 ambulatory PwMS were enrolled (68% females, 54±11 years, Patient Determined Disease Steps (PPDS) 2.9±1.9 [range; 0-7]). Participants were divided into one of two groups based on their $MSWS\text{-}12_{total}$-score (0-100). Group 1 were categorized as "no walking impairments" (NOWI; 0-37.49) and group 2 were categorized as having "walking impairments" (WI; 37.5-100), corresponding to an average answer of 2.5). Cut-points, Area Under the Curve (AUC), sensitivity (se), and specificity (sp) were identified using Receiver Operating Characteristic (ROC) curve analysis.

RESULTS: Based on 211 PwMS the following cut-points were identified between NOWI and WI for the 6MWT (446m; AUC=0.82, se=0.87, sp=0.78), SSST (0.113 rounds/s; AUC=0.76, se=0.77, sp=0.74 (corresponding to 8.8 seconds)) and T25FWT (1.39 meter/s; AUC=0.79, se=0.89, sp=0.69 (corresponding to 5.5 seconds)).

DISCUSSION: Using ROC-curve analysis, clinically relevant cut-points were identified for 6MWT (446m), SSST (8.8s), and T25FWT (5.5s) based on patient-reported walking ability. These cut-points provide novel insight on how to interpret different aspects of walking capacity in PwMS for use in clinical practice and research.

Effekten af IVF-behandling på MS sygdomsaktivitet

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HYPOTESE: Kvinder, der undergår in vitro fertilisation (IVF) efter at have fået stillet diagnosen multipel sklerose (MS) har en forhøjet attakrate i forhold til året før deres fertilitetsbehandling.

METODER: I dette registerstudie har vi sammenkørt Det Danske Scleroseregister med data fra IVF-registret. Studiepopulationen omfatter 162 kvinder med attakvis MS, der har modtaget mindst én IVF-behandling i perioden 1995-2018, med mindst ét år imellem diagnosetidspunktet for MS og første IVF-behandling. For kvinder, der har fået mere end én IVF-behandling, indgår de i dette studie med deres første IVF-behandling. Ved brug af negative binomiale regressionsmodeller, beregnede vi årlige attakrater (ARR) i tre tidsperioder: 1) de 12 måneder før IVF-behandling, 2) de første tre måneder efter IVF-behandling, og 3) de første ni måneder efter IVF-behandling. Vi sammenlignede ARR før med ARR efter IVF-behandling.

RESULTATER: Medianalder var 33 år (IQR 30-37) og kvinderne havde en gennemsnitlig MS sygdomsvarighed på 7,7 år (SD 4,5). Ved tidspunktet for den første IVF-behandling var median Expanded Disability Status Scale (EDSS) score på 1,5 (IQR 1,0-2,5). 37,6 % (N=61) modtog ingen sygdomsmodificerende behandling (DMT) før første IVF-behandling, 28,4 % stoppede DMT inden første IVF-behandling og 34,0 % fortsatte DMT under IVF-behandlingen.

ARR var 0,17 (95 % CI 0,11;0,26) de 12 måneder før IVF-behandlingen. Fra IVF-behandlingen til tre måneder efter IVF-behandlingen var ARR på 0,17 (95 % CI 0,08;0,36), og i perioden på de første ni måneder efter IVF-behandlingen var ARR 0,13 (95 % CI 0,08;0,23). Forskelle i ARR fra før til efter IVF-behandlingen var ikke statistisk signifikante.

Ved stratifikation på brug af DMT før IVF (ingen DMT, stop med DMT før IVF eller fortsat brug af DMT ved IVF) samt på typen af hormonstimulering ved IVF-behandlingen (kort eller lang behandling med Gonadotropin releasing hormone) var der heller ingen statistisk signifikante forskelle i ARR før og efter IVF.

DISKUSSION: Kvinder med MS, der undergår IVF-behandling, har ikke et højere niveau af sygdomsaktivitet i op til ni måneder efter IVF-behandling, sammenlignet med deres niveau for sygdomsaktivitet året før IVF-behandling. Vores landsdækkende studie bidrager med vigtig indsigt, ved at belyse at IVF-behandling anses som værende sikker for kvinder med MS og fertilitetsproblemer.

Perifere T-celle-responser under B-celle-fjernelse hos multipel sklerose patienter.

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HYPOTESE: Vores hypotese er, at terapeutisk fjernelse af perifere B-celler vil føre til forandringer i proliferation (celledeling) og cytokinproduktion hos T-celle subpopulationer.

METODER: Vi har isoleret PBMC (mononukleare immunceller fra blodet) fra multipel sklerose (MS)-patienter på forskellige tidspunkter efter anti-CD20-behandling: akut fjernelse (3 uger efter behandlingsstart), immunrestitution (lige før 2. behandlingscyklus) og fuld fjernelse (8 måneder efter den 1. behandlingscyklus). Prøver, der blev indsamlet før anti-CD20-behandling, blev sammenlignet med prøver fra matchende kontroller. PBMC blev stimuleret med en anti-CD3/CD28 cocktail i 3 dage efter mærkning med CFSE. Dette blev kombineret med forskellige antistoffarvninger for at måle proliferationscyklusser af T-celle subpopulationer. Cytokinproduktionen blev målt ved flerfarvet flow-cytometri med intracellulær staining af cellerne.

RESULTATER: Efter stimulering af PBMC med forskellige koncentrationer af anti-CD3/CD28 i 3 dage observerede vi en koncentrationsafhængig proliferation af forskellige T-celle subpopulationer. Både $CD4^+$ og $CD8^+$ T-celler proliferererede. Procentdelen og antallet af udmattede $PD\text{-}1^+$ T-celler steg på baggrund en øget koncentration af stimulans. Vi observerede også en øget proliferation af Tregs som følge af øget stimuli. Når PBMC blev stimuleret med anti-CD3/CD28 over natten og herefter restimuleret med PMA/Ionomycin, kunne vi detektere en koncentrationsafhængig stigning af IFN□, IL-2, IL-17a og IL-10.

DISKUSSION: Vi har succesfuldt etableret en protokol for kortvarig PBMC-kultur til at undersøge proliferation og cytokinproduktion hos T-celle subpopulationer. Vi analyserer de funktionelle ændringer hos PBMC isoleret fra blodprøver taget ved forskellige tidspunkter efter B-celle-fjernelse hos MS-patienter. Dette vil hjælpe med at karakterisere ændrede funktioner hos forskellige T-celle subpopulationer, samt deres ændringer i antal og procentdel.

Population-based national study of relapse-related outcomes in the aquaporin-4 seropositive NMOSD population.

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HYPOTHESIS/AIM: The disease course of aquaporin-4 antibody seropositive neuromyelitis optica spectrum disease (AQP4-Ab+ NMOSD) is unpredictable and highly variable. We aimed to examine relapse-related outcomes in AQP4-Ab+ NMOSD.

METHODS: Data from a nationwide retrospective cohort of 66 patients with AQP4-Ab+ NMOSD followed-up for 141.2 ±147.1 months were analyzed. Mixed-effects regression, logistic regression, and odds ratios (OR) were used to analyze association between relapse and maintenance treatment and expanded disability status scale (EDSS); type of relapse and its effect on the EDSS; type of initial relapse and risk of developing other types of relapses and frequency of relapses; age and relapse severity; and treatment and recovery.

RESULTS: Longer time before initiation of maintenance treatment correlated with higher EDSS scores at the last follow-up. Rituximab was the only maintenance treatment that correlated with a lower EDSS. Not receiving relapse treatment was associated with higher EDSS changes during the follow-up period. Brainstem (BS) relapses were the only type of relapses associated with a higher EDSS. There was a higher risk of developing optic neuritis (ON) after transverse myelitis (TM) (OR 1.17, 95%-CI: 0.54; 1.80, p <0.001) and to a lesser degree ***vice-versa*** (OR 1.07, 95%-CI: 0.50; 1.64, p <0.001). There was a slightly higher risk of BS relapse after TM (OR 1.02, 95%-CI: 0.19; 1.86, p = 0.016), while BS relapses were associated with decreased likelihood of developing TM (OR 0.88; 95%-CI: 0.08; 1.67, p = 0.031). ON was the only initial relapse type that correlated with a higher number of relapses at the last follow-up. Higher age and male sex were associated with more severe relapses of TM, and male sex was also associated with worse recovery after ON.

DISCUSSION: Earlier initiation of maintenance treatment can limit the accumulation of disability in NMOSD, especially when encountering BS relapses. Our findings indicate certain relapse patterns in NMOSD, which can aid the clinician in tailoring patient monitoring and treatment choice.

Biomarkers for tissue damage in inflammatory demyelinating diseases of the central nervous system

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HYPOTHESIS: Neurofilament light chain (NfL) and astrocyte glial fibrillary acidic protein (GFAP) are cytoskeletal proteins associated with axons and with astrocytes, respectively, and released into the cerebrospinal fluid (CSF) and serum following CNS injury. Recently our group reported microfibrillar-associated protein 4 (MFAP4) expression in the CNS. At sites of active inflammation, MFAP4 reactivity in tissue was reduced in acute stage and CSF MFAP4 levels were reduced during relapse. The potential association between MFAP4 and NfL and GFAP requires further investigation.

METHODS: We performed a cross-sectional, multicentre study involving 116 patients from six countries: 62 aquaporin-4-IgG (AQP4-IgG) positive neuromyelitis optica spectrum disorder (NMOSD), 21 myelin oligodendrocyte glycoprotein (MOG)-IgG-associated disease (MOGAD), and 33 patients with double seronegative (DS) disease, and age-matched healthy controls (CSF n=14 and serum n=64). Concentrations of NfL, GFAP and MFAP4 levels were measured by sensitive assays and correlated to the levels with disease activity and disease course.

RESULTS: The age of subjects did not differ between groups. Median duration from most recent relapse to lumbar puncture was 6 days (IQR 3- 21) for NMOSD, 11 (5-18) for MOGAD patients and 31 (15-39) for DS disease. In NMOSD the levels of NfL and GFAP were higher compared to DS disease ($p = 0.028$; $p = 0.000$). NfL and GFAP levels did not correlate with number of relapses or relapse severity for NMOSD and for all patients. Comparison between acute optic neuritis (ON) attack (n=35) and non-ON attacks (n=32) revealed higher levels of NfL for all patients ($p = 0.000$), and of GFAP for NMOSD ($p < .0001$) in the non-ON attacks.

The levels of NfL and GFAP in NMOSD patients were positively correlated (rho=0.35, p=0.032). CSF MFAP4 levels correlated with NfL levels in all patients (rho=0.21, p=0.0431) and with GFAP in NMOSD (rho=0.38, p=0.023),

DISCUSSION: The positive correlation between MFAP4, NfL and GFAP may reflect tissue damage in the CNS. In NMOSD correlation between GFAP and NfL may relate to the degree of astrocytopathy and neurodegeneration. Analysis of samples collected longitudinally may provide further insight into the value of these biomarkers.

Longitudinel billeddannelse af retinale hyperreflektive foci i multipel sklerose med optisk kohærens tomografi

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HYPOTESE: Hyperreflekterende foci eller prikker af usikker oprindelse med en diameter på 25-50 µm kan ses sporadisk i nethinden ved hjælp af optisk kohærens tomografi (OCT). Disse foci forekommer med lav frekvens og tæthed hos raske, men kan ses i forhøjede tætheder ved forskellige nethinde sygdomme. Histopatologi antyder, at de kan repræsentere mikroglia, en celletype, der mobiliseres ved forskellige sygdomme i centralnervesystemet (CNS), herunder multipel sklerose (MS). Hypotesen i dette studie var, at autoimmun CNS sygdom kan være ledsaget af forhøjet proinflammatorisk aktivitet i umyeliniserede dele af CNS.

METODER: I studiet undersøges forekomsten af hyperreflekterende foci i det ydre avaskulære kernelag af nethinden i 26 øjne hos 13 patienter med relapsing-remitting MS (RRMS) inklusiv 8 øjne med tidligere synsnervebetændelse. Baseline sammenligning blev foretaget ved en tværsnitsanalyse med 106 øjne hos 53 raske aldersmatchede kontrolpersoner. Højopløselig billeddannelse med OCT blev foretaget på alle patienter ved baseline, ved 1 og 6 måneder, og derefter hver 6. måned i 3 år. Ingen deltagere havde nogen klinisk påviselige nethindesygdomme. I alt blev 16855 B-scans inspiceret for tilstedeværelse af hyperreflektive foci i det ydre kernelag.

RESULTATER: Baseline prævalensen af hyperreflektive foci var 30,8% hos RRMS-patienter og 1,8% hos raske kontroller (p < 0,005). Median antallet af hyperreflektive foci ved baseline inden for RRMS-kohorten var 1(0-8) og hos raske kontroller 0 (0-2), (p < 0,005). Over den fulde 3-årige periode havde RRMS-patienter med synsnervebetændelse flere foci end dem uden synsnervebetændelse (p < 0,001). Af de i alt 69 foci var 69,5% lokaliseret inden for 3 mm fra maculas centrum. Hos 3 ud af 13 RRMS-patienter (23,1%) blev der observeret tilbagevenden af hyperreflektive foci på samme retinale placeringer.

DISKUSSION: Retinal infiltration med hyperreflekterende foci var hyppigere hos RRMS-patienter end hos raske og højere ved øjne med tidligere synsnervebetændelse. Hyperreflekterende foci var sjældne i begge grupper sammenlignet med det, der ses ved nethinde sygdomme. Vores observationer kan fortolkes som variationer i aktiviteten af overvågningsmekanismer snarere end en angrebsmekanisme med efterfølgende vævsskade. Det skal fortsat afgøres, om hyperreflekterende foci et særskilt fænomen eller en variant af et fænomen, der kun lejlighedsvis er forbundet med OCT-hyperreflektivitet.

One-year walking capacity changes in Danish patients with multiple sclerosis

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HYPOTHESIS: Change in walking capacity in persons with multiple sclerosis (pwMS) is an important efficacy marker in medical treatment, rehabilitation and research. However, as many different walking outcomes are used in MS research, little is known about measurement differences between the most frequently used outcomes. Thus, the present study aimed to compare one-year changes in walking capacity across three commonly used walking capacity outcomes in Danish MS patients following inpatient rehabilitation.

METHODS: In an observational two-hospital cohort study, walking capacity was assessed within the first week of inpatient rehabilitation (baseline (T1)) and after one year (T2) using the timed 25-foot-walk-test (T25FWT; "walking speed"), the six-minute-walk-test (6MWT; "walking endurance"), and the six-spot-step-test (SSST; "walking balance and coordination"). Using mixed linear models one-year relative within-group changes and effect sizes were compared across outcomes.

RESULTS: At T1 walking capacity was assessed in N=194 pwMS (69% females); age 54.3±11.4 yrs, patient determined disease steps (PDDS) 2.9±1.9, time since diagnosis 14.7±10.3 yrs and MS-phenotype (RRMS/SPMS/PPMS) 62%/18%/20%. At T2, results from 171 (88%) pwMS were available with mean improvements observed across all walking capacity outcomes; T25FWT +0.11 [0.07;0.15] (m/s), 6MWT +8 [-1;17] (m), and SSST 0.009 [0.004;0.013] (rounds/sec.). Relative within-group changes were improved for T25FWT (8.1 [1.3;15.0] %, Z-score=0.21) and SSST (7.7 [-1.1;16.6] %, Z-score=0.16), whereas 6MWT remained stable (2 [-5;8] %, Z-score=0.05). No within-group changes were observed across the three outcomes (p>0.10) and no improvements reached clinical meaningful thresholds.

DISCUSSION: Minor one-year improvements in walking capacity were observed across three commonly used walking capacity outcomes in Danish MS patients following two-three weeks of inpatient rehabilitation. Relative changes were similar across walking capacity outcomes but did not reach clinically meaningful thresholds. MS patients sustained their walking capacity, which is considered important in progressive diseases.

Effects of MS Ballroom Fitness TM perceived by people with Multiple Sclerosis – a qualitative study.

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HYPOTHESIS: The importance of physical exercise for people with Multiple Sclerosis (pwMS) is well documented. However, as MS is often accompanied by fatigue and other energy-based challenges, the motivational factor constitutes a widespread barrier for exercise. More knowledge on interventions that combine exercise and motivational factors, e.g., music-based interventions, is needed.

An MS-specific dance/fitness intervention was developed and tested in a cluster randomized controlled study design. Subsequently, an interview study was conducted to investigate the perceived outcomes as well as various factors linked to the obtaining of outcomes.

METHODS: Among 91 pwMS, participating in a 7-week dance/fitness intervention, 12 informants were randomly selected and included in an interview study. Qualitative interviews were performed based on an interview guide and within a program theoretical framework, elucidating the informants' perceived outcomes as well as their perspectives on associations between the intervention, the mechanisms of action, the contextual factors, and the outcomes.

RESULTS: The informants consistently described the intervention as being characterized by high motivation and multifaceted stimulation of functions. The intervention was experienced as a highly relevant and motivating combination of music, rhythm, coordinated movements, exercise, and social interaction in a safe environment with good atmosphere. This leading to stimulation and strengthening of various functions on a direct level (positive outcomes most often mentioned were balance, mood, coordination, and cognition) as well as on a process-oriented indirect level, supporting general activities as well as supplemental exercise initiatives in an everyday perspective.

DISCUSSION: A 7-week intervention of MS Ballroom Fitness™ was by the involved pwMS perceived as a very relevant exercise intervention, characterized by a high level of motivation and a multifaceted stimulation of functions, leading to a broad range of direct as well as indirect/process-oriented outcomes.

Severe acute respiratory syndrome coronavirus 2 antibodies in relapsing-remitting multiple sclerosis patient undergoing CD20-depleting therapy

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HYPOTHESIS: Multiple sclerosis (MS) is a chronic demyelinating disease associated to the central nervous system (CNS). It has been speculated that immune mechanisms induced by severe acute respiratory syndrome coronavirus-2 (SARS-CoV-2), may play a role in the clinical onset of MS, by triggering an exacerbation of inflammatory disease. Based on this we evaluated the SARS-CoV-2 antibody status in relapsing-remitting MS (RRMS) patients and the effect of CD-20-depleting therapy on SARS-CoV-2 antibody levels.

METHODS: IgG to spike protein from SARS-CoV-2 were examined in serum samples from RRMS patients (n = 27) and healthy controls (HCs) (n=15) by enzyme-linked immunosorbent assay. In total, 27 RRMS patients donated 42 serum samples, 13 samples were collected at baseline prior to CD-20-depleting ocrelizumab therapy, whereas 29 serum samples were collected during routine follow-up. RRMS patients (F:M 16:10, 41.94 years) and HCs (F:M 10:5, 42.15 years) were sex- and age-matched when possible. Moreover, cerebrospinal fluids (CSF) from 11 RRMS patients (F:M 8:3, 40.63 years) were screened for antibodies to spike protein as well, to determine whether RRMS patients had SARS-CoV-2-specific intrathecal antibody synthesis in the CNS.

RESULTS: No difference in IgG titers to spike protein were observed between HCs and RRMS at baseline. IgG titers were significantly reduced after 6 (p = 0.0143) and 12 months (p = 0.0155) of treatment when compared to HCs. Moreover, approximately 20% of RRMS patients were positive for intrathecal antibody synthesis to spike protein presenting with an antibody index above 1.5.

DISCUSSION: These findings indicate that RRMS patients present with SARS-CoV-2 spike protein antibodies primarily in serum but occasionally in the CSF as well, indicating that B-cells producing antibodies to spike protein have entered the CNS, which is a typical sign of inflammation. Moreover, at baseline, RRMS patients did not express elevated SARS-CoV-2 spike protein antibodies when compared to HCs, in fact CD-20-depleting treatment reduced the virus-specific IgG level when compared to HCs. A potential bias is that not all of the participating RRMS patient had been neither vaccinated nor exposed to SARS-CoV-2 infection at the time of sample collection, whereas all HCs were vaccinated or exposed to infection.

NOTER

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