

PROGRAM

Storebælt Sinatur Hotel & Konference
2. & 3. juni 2023

Nationalt MS Forskningsmøde 2023

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

Fredag 2. juni 2023

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- 9.00-10.00 ● **Registrering og Kaffe/te med hjemmebagt brød**
- 10.00-10.10 **Velkomst ved DAREMUS' bestyrelse (Formand Jeppe Romme)**
- 10.10-11.00 **DAREMUS lecture:** Prof. Per Soelberg Sørensen, DMSC Rigshospitalet – *Klinisk og translational MS forskning i Danmark*
- 11.00-12.00 **MS Forskningstalent-priserne 2023**
Chairs: Tobias Sejbæk og Viktoria Papp
- 11.00-11.12 Maria Louise Elkjær; OUH – *Integreret cellulære og molekylære teknikker identificerede mekanistiske programmer i MS læsioner*
- 11.12-11.24 Malthe Wandall Holm; RH – *Fingolimod behandlingsstop medfører høj risiko for nye T2-læsioner: Et landsdækkende prædiktivt og komparativt studie.*
- 11.24-11.36 Frederik Novak Stenstad; Esbjerg – *Forlænget behandlingsinterval med ocrelizumab hos patienter med multipel sklerose*
- 11.36-11.48 Sahla El Mahdaoui; RH – *Perifere og intratekale CD11c+ B celler ved atakvis multipel sklerose og effekt af anti-CD20 monoklonal antistof behandling*
- 11.48-12.00 Mark Bitsch Vestergaard; RH – *Patients with multiple sclerosis have impaired cerebrovascular and cerebral oxygen metabolic response to hypoxic exposure*
- 12.00-13.30 **Videnskabelig session: Klinisk forskning**
Chairs: Zsolt Illes og Annika Langkilde
- 12.00-12.30 Keynote lecture: Jaqueline Palace, University of Oxford – *Differentiating MS, NMOSD and MOGAD*
- Præsentation af udvalgte abstracts**
- 12.30-12.42 Jette Frederiksen, RH – *The potential contribution of MRI of the optic nerve to the McDonald Criteria for multiple sclerosis.*
- 12.42-12.54 Viktoria Papp, OUH – *Population-based mortality data of the Danish nationwide AQP4 antibody-seropositive NMOSD cohort*
- 12.54-13.06 Elisabeth Framke, RH – *Risiko for hjertekarsygdom blandt patienter behandlet med fingolimod sammenlignet med natalizumab: Et landsdækkende kohortestudie i Danmark*
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Program for DAREMUS nationalt forskningsmøde 2023 med de nyeste resultater indenfor dansk forskning i multipel sklerose. Mødet er arrangeret i samarbejde med Dansk Multipel Sklerose Center (Rigshospitalet) og er sponsoreret af Scleroseforeningen samt Alexion, Biogen, Merck, Novartis, Roche, Sandoz og Sanofi.

13.06 – 13.18	Rolf Pringler Holm, RH – <i>Socioøkonomisk diskrepans mellem ældre patienter med MS og baggrundsbefolkningen – et nationalt tværsnitsstudie</i>
13.18 – 13.30	Tobias Sejbæk, Esbjerg – <i>Diskontinuationsrater under behandling med dimethyl fumarat hos patienter med multipel sklerose – et nationalt kohortestudie</i>
13.30 – 14.30	● Frokost
14.30 – 15.00	● Kaffepause
15.00 – 16.30	Videnskabelig session: Basal og eksperimentel forskning Chairs: Jeppe Romme Christensen og Reza Khorrooshi
15.00 – 15.30	Keynote lecture: Trevor Owens, SDU – <i>Neuroinflammation in MS and autoimmune neurological disorders</i>
	Præsentation af udvalgte abstracts
15.30 – 15.42	Christina Kingo, OUH – <i>Expression of Bruton's tyrosine kinase in brain of MS patients and during experimental demyelination</i>
15.42 – 15.54	Moschoula Passali, RH – <i>Ryggestatus i relation til væske-biomarkører hos patienter med akut synsnervebetændelse</i>
15.54 – 16.06	Niels Koch-Henriksen, AUH – <i>Udfordringer ved estimering af effekten af sygdoms-modificerende behandling ved MS i åbne observationsstudier.</i>
16.06 – 16.18	Astrid Meng Andersen, AUH – <i>Higher disability status is associated with substantial negative alterations of physical activity levels in persons with multiple sclerosis</i>
16.18 – 16.30	Zsolt Illes, OUH – <i>New enhancing MRI lesions associate with IL-17, neutrophil degranulation and integrin microparticles: multi-omics combined with frequent MRI</i>
16.30 – 16.45	● Strække-ben pause
16.45 – 18.15	Poster-session og forfriskning
19.00 – 21.00	Middag inkl. uddeling af DAREMUS priser

Lørdag 3. juni 2023

9.00-10.00	Klinisk program – MS rehabilitering, sygepleje og symptomatisk behandling Chairs: Henrik Boye Jensen og Morten Blinkenberg
9.00-9.30	Ulrik Dalgas, AU – <i>Effekter af fysisk træning ved multipel sklerose</i>
	Præsentation af udvalgte abstracts
9.30-9.42	Lars Hvid, Sclerosehospitalerne – <i>Comprehensive evaluation of self-management skills following multidisciplinary rehabilitation in persons with MS – The Danish MS Hospitals Rehab Study</i>
9.42-9.54	Anders Gulddammer Skjerbæk, Sclerosehospitalerne – <i>Substantial deficits and differences exist across measures of walking capacity in patients with multiple sclerosis</i>
10.00-10.20	● Kaffepause
10.20-11.10	Klinisk program – MS diagnostik og epidemiologi Chairs: Melinda Magyari og Peter Vestergaard Rasmussen
10.20-10.50	Jan Hillert, Karolinska Instituttet – <i>Udfordringer i diagnostik og behandling af SPMS</i>
	Præsentation af cases
10.50-11.00	Karin Holst Lauridsen, RH – <i>Differentiering mellem MOGAD og multiple sklerose</i>
11.00-11.10	Zuhal Filikci, RH – <i>Langstrakt transversel myelit (LETM) hos 30-årig kvinde med familiær disposition til multipel sklerose (MS)</i>
11.10-12.00	Klinisk program – MS behandling (Chairs: Melinda Magyari og Peter Vestergaard Rasmussen)
11.10-11.40	Finn Sellebjerg, RH – <i>Analyse af blod neurofilament til behandlingsvalg- og monitorering</i>
	Præsentation af cases
11.40-11.50	Frederik Novak Stenstad, Esbjerg – <i>Forlænget doseringsinterval ved behandling med natalizumab</i>
11.50-12.00	Betul Okutan, RH – <i>Neoehrlichiose hos patient med atakvis multipel sklerose i B-celledepleterende behandling</i>
12.00-13.00	● Frokost
13.00-13.45	DMSG møde
13.45-14.30	Generalforsamling DAREMUS

Abstracts



Videnskabelige foredrag

Integreret cellulære og molekylære teknikker identificerede mekanistiske programmer i multipel sklerose læsioner

FORFATTERE: Elkjaer Maria Louise^{1,2,3}, Har-tebrodt Anne⁴, Oubounyt Mhaned⁵, Weber Anna^{1,2,3}, Vitved Lars³, Reynolds Richard^{6,7}, Thomassen Mads^{2,8}, Rottger Richard⁹, Baumbach Jan^{5,9}, Illes Zsolt^{1,2,3}

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HYPOTESE: Vores hypotese er, at vi med integration af de nyeste celle- og molekylære teknikker kan undersøge og afdække tre grundlæggende spørgsmål i progressiv MS. Tre spørgsmål, hvis svar kan føre til en bedre forståelse af de ellers uforklarlige sygdomsmekanismer i hjernen hos progressiv MS. (1) Hvilke gener er aktiveret af forskellige celletyper i hjernelæsioner hos progressiv MS? (2) Hvordan er de regulatoriske cellemekanismerne programmeret? (3) Hvor befinder disse celler sig i hjernelæsionerne?

METODER: Vi undersøgte hver enkelt celle ud af >80,000 celler i 15 mikrodisekterede hjerneområder fra progressive MS-patienter og kontroller for integrerede forskelle i genaktivering (snRNA-seq) og regulatoriske

ændringer (snATAC-seq) kombineret med deres placering i hjernen (spatial transcriptomics). Vi fandt differentielle genetiske profiler fra identificerede celletyper ved blandt andet quasi-likelihood pipeline (edgeR-quasi) og weighted gene coexpression network analysis (WGCNA).

RESULTATER: I MS-læsionerne fandt vi en højere tilgængelighed af SP/KLF transkriptionsfaktorer i oligodendrocytter, der kontrollerer mekanismer for myelinisering og stress-induceret jernoptag. Vi fandt også øget jernoptag via oligodendrocyt-kommunikation med deres transferrin-megalin molekyler, samt oligodendrocytter producerede proinflammatoriske molekyler som osteopontin og komplement faktorer ved grænsen til den kroniske aktive MS-læsion. I den kroniske aktive læsion var den kliniske neuronale biomarkør (NFL) tilstede, og vi fandt en neuronal-astrocyt-akse, der indbyrdes kommunikerede gennem vækstsIGNALERING (FGF13-FGFR3). Astrocytter havde høj metabolisk aktivitet i kanten af den kroniske aktive læsion, og samtidig var der aktivering af arvævsprocesser, der kunne tyde på, at astrocytter spreder sig for at afskærme inflammationen i læsionen fra det normale væv. Desuden identificerede vi to B-celletyper, hvis gener kunne adskille MS-patienter fra kontroller i et større kohorte. De andre immunceller i læsionerne kommunikerede til andre celler med komplementfaktorer og apolipoproteiner og var karakteriseret ved et MAFB-drevet genmodul i MS-læsioner.

DISKUSSION: Via et innovativt, omfattende og detaljeret multi-molekylært informationslag fra enkelte hjerneceller i progressiv MS fik vi et øjebliksbillede af specifikke celletyper med særskilte molekylære signaturer og signalveje samt deres interaktioner og placeringer – alt sammen noget der bidrager til læsionens skæbne. Vores tilgang og fund kan således være afgørende for at komme nærmere en forståelse af de mekanismer bag læsionsudvikling fra progressiv MS, som kan hjælpe til forbedret behandling.

Fingolimod behandlingsstop medfører høj risiko for nye T2-læsioner: Et landsdækkende prædiktivt og komparativt studie.

FORFATTERE: Wandall-Holm Malthe Faurshou¹; Holm, Rolf Pringler¹; Heick, Alex²; Magyari, Melinda^{1,2}

INSTITUTION: ¹Danish Multiple Sclerosis Registry, Department of Neurology, Copenhagen University Hospital – Rigshospitalet, Glostrup, Denmark. ²Danish Multiple Sclerosis Center, Department of Neurology, Copenhagen University Hospital – Rigshospitalet, Glostrup, Denmark

HYPOTESE: Fingolimod er en hyppig brugt sygdomsmodificerende behandling mod attackvis sklerose. Kasuistikker og små observationelle studier har indikeret tilstedeværelsen af en kraftig sygdomsaktivering i forbindelse med behandlingsstop. Formålet med studiet var at undersøge radiologisk sygdomsaktivitet efter behandlingsstop med fingolimod.

METODER: Vi udførte et landsdækkende kohortestudie ved brug af Det Danske Scleroseregister. Vi inkluderede patienter, der stoppede fingolimod eller dimethyl fumarat mellem januar 2014 og 2023, havde attackvis sklerose og to MR-scanninger indenfor henholdsvis et år før og efter behandlingsstop. De to behandlingsgrupper blev herefter sammenlignet i en ujusteret og en propensity-score baseret analyse for at vurdere sandsynligheden for nye T2-læsioner (NT2L) på MR-scanningen efter behandlingsstop. Som underanalyse lavede vi en prædiktiv model i en fingolimod-subpopulation med det formål at identificere patienter i særlig høj risiko for NT2L.

RESULTATER: Ud af 1324 patienter med fingolimod-behandlingsstop i studieperioden inkluderede vi 752 patienter (gennemsnitlig alder [SD], år, 41 [10]; 552 kvinder [73%]; median EDSS [IQR], 2.5 [2.0–3.5]; gennemsnitlig sygdomsvarighed [SD], år, 12 [8]). Ud af 2044 patienter med dimethyl fumarat-behandlingsstop inkluderede vi 957 patienter med lignende kliniske karakteristika. I fingolimod-populationen havde 127 [17%] 1-2 NT2L

og 124 [17%] ≥ 3 NT2L sammenlignet med respektivt 114 [12%] og 45 [5%] i dimethyl fumarat-population svarende til odds-ratioer [95% CI] på 1.8 [1.3–2.4] og 4.4 [3.1–6.3] i den ujusterede analyse. Den propensity-score baserede analyse havde enslydende resultater. Den prædiktive model indeholdt 509 af de oprindelige 752 fingolimod-patienter og viste en forøget risiko for NT2L blandt kvinder under 40 samt patienter med sygdomsaktivitet under fingolimod behandling.

DISKUSSION: Dette landsdækkende studie viser, at behandlingsstop med fingolimod er forbundet med en betydelig risiko for ny radiologisk sygdomsaktivitet. Klinikere bør udvise forsigtighed i denne population samt overveje andre behandlinger til kvinder i den fødedygtige alder.

Forlænget behandlingsinterval med ocrelizumab hos patienter med multipel sklerose

FORFATTERE: Novak, Frederik^{1,2}; Bajwa, Hamza Mahmood^{1,2}; Østergaard, Kamilla³; Berg, Jonas Munksgaard⁴; Madsen, Jonna Skov²; Olsen, Dorte Aalund⁵; Urbonaviciute, Inga⁶; Sellebjerg, Finn⁷; Illes, Zsolt⁸; Stilund, Morten⁹; Sejbaek, Tobias^{1,2}

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HYPOTESE: Forlænget behandlingsinterval med ocrelizumab hos patienter med MS kan føre til øget sygdomsaktivitet. I dette studie undersøges sygdomsaktivitet ved standard- og forlænget behandlingsinterval med ocrelizumab.

METODE: I alt blev 183 deltagere fra syv MS-klinikker i Danmark inkluderet i et prospektivt, dobbeltarmet kohortestudie. Inklusionskriterierne var minimum 12 måneders forudgående ocrelizumab behandling for MS. Deltagerne blev inkluderet fra maj 2020 og fulgt frem til december 2021, med neurostatus og MR-scanning. Blodprøve ved inklusion blev analyseret for NFL, GFAP, ocrelizumab, autoantistoffer mod ocrelizumab og B-celler. Standard behandlingsinterval blev defineret som 24–28 uger og forlænget behandlingsinterval som >28 uger. Der blev anvendt non-parametrisk statistik og korrelationsanalyser med univariabel lineær regression. Der blev foretaget cox regression analyser og beregnet hazard ratio med Mantel-Haen-

zel test.

RESULTATER: 107 deltagere blev behandlet med forlænget interval (gennemsnit: 35.1 uger; SD: 6.3, range: 29.0–78.1 uger) og 76 deltagere blev behandlet indenfor standardinterval (gennemsnit: 26.1 uger; SD: 1.2; range: 21.9–28.4 uger). Der var ikke forskel på niveauet af NFL ($p=0.08$) og GFAP ($p=0.62$) i de to behandlingsgrupper. B-celle niveauer hos deltagere med forlænget behandlingsinterval var højere end hos deltagere med standard behandlingsinterval, henholdsvis 0.038 (SD: 0.050) og 0.007 (SD: 0.018) ($p<0.00001$). Der var ingen sammenhæng imellem NFL-, GFAP-niveauer og behandlingsinterval. Regressions analyser fandt en sammenhæng imellem behandlingsinterval og B-celle niveauer ($R=0.35$, $p<0.0001$). Survival analyser for attack og nye MS-læsioner viste en hazard ratio på 0.93 (95% CI: 0.41–2.10, $p=0.86$) og confirmed disability worsening viste ingen forskel mellem de to grupper, hazard ratio på 1.04 (95% CI: 0.20–5.50, $p=0.96$). Survival analyse for NEDA-3 viste ingen sammenhæng mellem standard- og forlænget behandlingsinterval, hazard ratio 1.17 (95% CI: 0.53–2.59, $p=0.59$). Koncentrationer af ocrelizumab og autoantistoffer overfor ocrelizumab vil blive præsenteret på konferencen.

DISKUSSION: Dette danske multicenter studie har undersøgt forskellen på standard- og forlænget behandlingsinterval med ocrelizumab hos patienter med MS. Resultaterne viser forskelle i B-celle niveauer men i øvrigt ingen forskel på almindelige kliniske endepunkter, NEDA-3 eller biomarkører i blod. Der er behov for yderligere studier til at undersøge om forlænget behandlingsinterval med ocrelizumab kan anvendes under langtidsbehandling af multipel sklerose.

Perifere og intratekale CD11c⁺ B celler ved atakvis multipel sklerose og effekt af anti-CD20 monoklonal antistof behandling

FORFATTERE: El Mahdaoui, Sahla¹; Hansen, Marie Mathilde¹; von Essen, Marina¹; Hvalkof, Victoria Hyslop¹; Sellebjerg, Finn¹; Romme Christensen, Jeppe¹

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HYPOTESE: Behandling med anti-CD20 monoklonale antistoffer (mAb) har markant effekt på sygdomsaktiviteten ved atakvis multipel sklerose (RRMS), hvilket understreger en central rolle for B celler i immunpatogenesisen. Det er endnu uvist, om behandlingseffekten kan relateres til depletion af specifikke pro-inflammatoriske undergrupper af B celler, og studier af effekten af anti-CD20 mAb på cerebrospinalvæske (CSV) B celler er begrænsede. CD11c⁺ B celler er en undergruppe af B celler, som øges i frekvens med alder, efter virusinfektioner og ved autoimmune sygdomme, og som er blevet foreslået som patogener ved inflammatoriske sygdomme. CD11c⁺ B celler i blod er i nogle studier antydende at være relativt resistente for anti-CD20 mAb behandling. Studiets hypotese er, at anti-CD20 mAb behandling medfører reduktion af B celler i blod og CSV, og at CD11c⁺ B celler er relativt resistente for B celle depletion.

METODER: Observationelt tværsnits-studie af 27 behandlingsnaive personer med RRMS, 24 personer med RRMS behandlet med ocrelizumab eller rituximab i 6 måneder, og 17 kontroller (12 symptomatiske kontroller og 5 med non-inflammatorisk neurologisk sygdom). Vi anvendte flowcytometrisk analyse til undersøgelse af CD19⁺CD11c⁺ B celler i blod og CSV.

RESULTATER: Som forventet var andelen af B celler i blod meget lav for anti-CD20 mAb behandlede (medianfrekvens 0.14%) til sammenligning med behandlingsnaive (9%, p<0.01) og kontroller (8%, p<0.01). Frekvensen af CD11c⁺ B celler i blod var højere hos anti-CD20 mAb behandlede (medianfrekvens 56%) end behandlingsnaive (9%, p<0.01) og

kontroller (8%, p<0.01). Behandlingsnaive havde flere celler i CSV (median 8 celler/μL) end anti-CD20 mAb behandlede (2 celler/μL, p<0.01) og kontroller (2 celler/μL, p<0.01), mens andelen af B celler i CSV var ens (medianfrekvens 2%). Behandlingsnaive havde lavere procentdel CD11c⁺ B celler i CSV (medianfrekvens 32%) end anti-CD20 mAb behandlede (86%, p<0.01) og kontroller (88%, p<0.01).

DISKUSSION: Studiet indikerer, at CD11c⁺ B celler er relativt resistente overfor anti-CD20 mAb behandling, særligt i CSV. Et overraskende fund er, at B celler i CSV hos kontroller i høj grad er CD11c⁺. Yderligere studier er nødvendige for at afklare CD11c⁺ B cellers funktionelle egenskaber ved MS, og om der er en relation mellem behandlingseffekt af anti-CD20 mAb og frekvensen af CD11c⁺ B celler.

Patients with multiple sclerosis have impaired cerebrovascular and cerebral oxygen metabolic response to hypoxic exposure

FORFATTERE: Vestergaard, Mark B.¹, Passali, Moschoula², Cramer, Stig P.¹, Frederiksen Jette L.^{2,3}, Larsson, Henrik B.W.^{1,3}

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Hypothesis: Patients with multiple sclerosis (MS) demonstrate cerebral atrophy that accelerates as the disease progresses. Pathways for this atrophy have not been fully established. A link could be through a cerebrovascular dysfunction from inflammatory processes harming the cerebral endothelium functions reducing the vasomotor capability. Studies on post-mortem brain cells have also demonstrated hypoxia-like damage in MS patients, suggesting a physiological malfunction. We tested this hypothesis by measuring the response in cerebral blood flow (CBF), metabolic rate of oxygen (CMRO₂) and lactate concentration to a hypoxic challenge.

METHODS: 27 MS patients (23 relapsing-remitting MS and 4 secondary progressive MS, age=49.1±7.7 years, 19 females, disease duration=13.1±8.3 years, expanded disability status scale (EDSS)=3.7±1.6) and 22 healthy controls (age=44.7±13.7 years, 10 females) participated. The participants were examined by a single 3T MRI brain scan session. Global mean CBF was obtained by measuring the blood flow through the feeding cerebral arteries (the carotids and basilaris) using velocity-sensitive phase-contrast MRI. Global mean CMRO₂ was calculated by Fick's principle ($\dot{V}_O_2 = CBF \times (C_{aO_2} - C_{vO_2})$), using susceptibility-weighted MRI to measure the venous oxygen saturation of the blood leaving the brain in the sagittal sinus. Cerebral lactate concentration was measured by MR spectroscopy. CBF, CMRO₂ and lactate were measured at normoxia and

again during inhalation of hypoxic air (~12% oxygen content) for approximately 20–30 minutes.

RESULTS: The participants desaturated to 81.9±4.5% during inhalation of hypoxic air. Hypoxia increased CBF in both groups (0.37 and 0.67 ml blood/100g/min per % desaturation for patient and controls, respectively). The response in the patients was significantly diminished compared to controls (p=0.008). The controls maintained CMRO₂ during hypoxia (p=0.28), whereas the patients had a significant reduction of 1.1 mmol O₂/100g/min per % desaturation (p=0.038). Lactate concentrations increased significantly (p<0.001) in both groups but with no differences between the two (p=0.78). Baseline values of CBF, CMRO₂ and lactate were not significantly different between the groups (p>0.25).

DISCUSSION: Patients with MS demonstrate a reduced cerebrovascular function and an inability to maintain normal CMRO₂ during a hypoxic challenge. Cerebrovascular dysfunctions are also observed in dementia disease and could be a driver of the accelerated cerebral atrophy observed in MS.

The potential contribution of MRI of the optic nerve to the McDonald Criteria for multiple sclerosis.

FORFATTERE: Frederiksen Jette¹, Knudsen Maria¹, Simonsen Helle¹, Cramer Stig¹, Larsson HB¹, Passali Moschoula¹

INSTITUTION: ¹Clinic of Optic Neuritis and Functional Imaging Unit, Rigshospitalet Glostrup

HYPOTHESIS: The 2017 McDonald criteria for the diagnosis of multiple sclerosis (MS) are widely used in clinical practice and research (Thompson et al. Diagnosis of multiple sclerosis: 2017 revisions of the McDonald criteria. *Lancet Neurol* 2018). In patients experiencing a typical clinically isolated syndrome like optic neuritis (ON) MRI demonstration of dissemination in time and space of lesion are part of the diagnostic criteria of MS, but the optic nerve – although part of the central nervous system (CNS) – is not one of the 4 McDonald criteria based on lack of evidence. This study aims to examine the value of MRI of the orbit to potentially include MRI lesion of the optic nerve as a 5th McDonald criteria for MS.

METHODS: In the period from 2018 to 2021 51 patients referred with acute ON to The Clinic of Optic Neuritis at Rigshospitalet Glostrup had MRI of the orbit with contrast enhancement performed at the Philips Achieva 3T scanner in addition to MRI of the rest of the CNS. The age was median 31 years (IQR 26–39) and 30 were women, 21 men.

RESULTS: Of the 51 patients with MRI of the orbit, 46 had lesions in the optic nerve; 39 of these contrast enhancing lesions. The McDonald criteria also stress the need for no better explanation for the presentation, and in one patient with lesion in the optic nerve the cause showed up to be sarcoid. Of the 5 patients without optic nerve lesions one showed up to have NAION. Of the 46 patients with an optic nerve lesion at MRI only 1 of the 4 McDonald criteria were fulfilled in 8. Thus, by adding the optic nerve lesion at MRI to the McDonald criteria would increase the subgroup with MS by 8.

DISCUSSION: Diagnosis and classification of ON may be challenging, and MRI of the optic nerve is only one of several paraclinical tests of value and therefore not needed to perform in every patient with optic neuritis (Petzold A, et al. Diagnosis and classification of optic neuritis. *Lancet Neurol* 2022). However, our study supports the idea raised in the publication of the 2017 McDonald criteria for MS that research to further refine the criteria should focus on optic nerve involvement.

Population-based mortality data of the Danish nationwide AQP4 antibody-seropositive NMOSD cohort

FORFATTERE: Viktoria Papp¹, Melinda Magyar², Sören Möller³, Finn Sellebjerg², Jette L. Frederiksen², Kristina B. Svendsen⁴, Helle B. Søndergaard⁵, Anna C. Nilsson⁶, Zsolt Illes¹

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HYPOTHESIS: The mortality of AQP4 antibody-seropositive (Ab+) NMOSD in Denmark compared to the general population.

METHODS: We identified AQP4-Ab+ NMOSD patients fulfilling the 2015 IPND criteria from multiple sources (laboratories and the Danish Multiple Sclerosis Registry). We obtained detailed data about patients from hospital records and about the general population matched on age, sex and calendar year from Statistics Denmark. We calculated standardised mortality ratio (SMR), excess number of death per 1000 person-years (EDR) and life expectancies compared to the matched general population. We examined predictive factors of mortality and the cause of death.

RESULTS: Out of 66 AQP4-Ab+ NMOSD patients, 15 died between 2008 and 2020. The median follow-up time of those who died was 89 months (IQR:24-182) and for patients alive 101 months (IQR:55-173). Median life expectancy for patients was 64.08 years (95% CI:53.02-83.9), compared with 83.07 years for the general population. The patient year of observation was 542 years resulting

in an EDR of 16.8 per 1000 person-years (95% CI:4.6-34.3). Overall, SMR was 2.54 (95% CI: 1.47-4.09). The cumulative probability of survival from disease onset was 90.2% (95% CI:79.4-95.5) for 5 years and 82.9% (95% CI:69.2-91%) for 10 years. Risk of death over time was higher in the patient population with HR of 2.22 (1.34-3.68; p=0.002). Significantly higher median EDSS was reported in the deceased cases during follow-up and at the last follow-up or before death. The cause of death was directly related to NMOSD in 93% of the cases. Three (20%) out of 15 patients died within six months after the first attack. The age of onset was an independent predictor of death (HR:1.043; 95% CI:1.006-1.079; p=0.02).

DISCUSSION: AQP4-Ab+ NMOSD is associated with increased mortality and shorter life expectancy compared to the general population indicating the need for highly effective treatment approaches.

Risiko for hjertekarsygdom blandt patienter behandlet med fingolimod sammenlignet med natalizumab: Et landsdækkende kohortestudie i Danmark

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HYPOTESE: Formålet var at undersøge den langsigtede sikkerhedsprofil i forhold til hjertekarsygdom blandt patienter med multipel sclerose (MS) behandlet med fingolimod, og hypotesen var, at patienter behandlet med fingolimod var i højere risiko for at udvikle hjertekarsygdom sammenlignet med patienter behandlet med natalizumab.

METODER: Vi har gennemført et landsdækkende kohortestudie ved at koble pseudo-anonymiserede individdata fra Det Danske Scleroseregister med Landspatientregistret, Lægemedelstatistikregistret, Dødsårsagsregistret og Det Centrale Personregister. Eksponeringen for fingolimod henholdsvis natalizumab blev defineret ved første behandling af mindst tre måneders varighed med inklusionsperiode fra 2011 til 2018. Hjertekarsygdom blev defineret som et kombineret udfaldsmål bestående af hypertension, atrieflimren og iskæmisk hjertesygdom baseret på hospitalskontakter og lægemiddelforbrug. Patienter med udfald før opfølgningen blev ekskluderet. Vi anvendte overlevelsesanalyse justeret for køn, alder og kalenderår for inklusion i kohorten. Opfølgningstiden startede efter tre måneders behandling og varede hele behandlingen plus et år mere, dog senest til 1. marts 2023. Analyserne censureredes for emigration og død af andre årsager end hjertekarsygdom.

RESULTATER: I alt indgik 2126 patienter i studiet, heraf 1145 fingolimod- og 981 natalizumab-behandlede. Henholdsvis 66% (N=750, fingolimod) og 69% (N=680, natalizumab) var kvinder. Ved opfølgningsperiodens start var fingolimod-behandlede patienter i gennem-

snit 38,8 år (SD=9,2) og havde en gennemsnitlig sygdomsvarighed på 8,4 år (SD=6,6), hvor natalizumab-behandlede patienter i gennemsnit var 36,9 år (SD=9,5) og havde en gennemsnitlig sygdomsvarighed på 7,2 år (SD=6,7). Gennemsnitligt niveau i årlige attackter ved opfølgningsstart var 0,8 (SD=0,8) og 0,9 (SD=0,9) i fingolimod- henholdsvis natalizumab-gruppen, og medianen i EDSS scorer var 2,0 (IQR: 1,5;3,0, fingolimod) og 2,5 (IQR: 1,5;3,5, natalizumab). I løbet af 10.345 person-år var der 243 nye tilfælde af hjertekarsygdom, 28,0 per 1000 person-år (fingolimod-gruppen) og 17,3 per 1000 person-år (natalizumab-gruppen). Resultaterne viste, at fingolimod-behandling, sammenlignet med natalizumab-behandling, var forbundet med en 1,54 gange højere risiko for hjertekarsygdom (hazard ratio=1,54; 95% konfidensinterval=1,17-2,03).

DISKUSSION: Patienter med MS uden eksisterende hjertekarsygdom i behandling med fingolimod har en højere risiko for at udvikle hjertekarsygdom. Disse resultater har kliniske implikationer, hvor læger bør overveje patientens risikoprofil og mulige bivirkninger ved behandling med fingolimod.

Socioøkonomisk diskrepans mellem ældre patienter med MS og baggrundsbefolkningen – et nationalt tværnsnitsstudie

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HYPOTESE: Projektets formål var at beskrive kliniske og socioøkonomiske parametre i den aldrende danske befolkning med multipel sklerose (MS) og holde det op imod baggrundsbefolkningen. Hypotesen var, at MS-befolkningen klarer sig betydeligt dårligere end baggrundsbefolkningen på en lang række socioøkonomiske parametre.

METODER: Vi udførte et matchet tværnsnitsstudie med alle nulevende patienter med MS \geq 50 år bosiddende i Danmark 1. januar 2021. Patienterne blev matchet 1:10 på køn, alder og bopæl med personer fra en 25%-stikprøve af den danske befolkning. Demografiske og kliniske karakteristika blev indhentet fra Det Danske Scleroseregister, og socioøkonomiske data blev indhentet fra andre landsdækkende offentlige registre. Vi viste alder ved debut af MS, fænotype, Expanded Disability Status Scale score, attackaktivitet og data om evt. medicinske behandlinger for hele den aldrende MS-population. Derefter sammenlignede vi flere demografiske og socioøkonomiske parametre med den matchede population: Vi undersøgte socioøkonomiske forhold som civilstand, uddannelsesniveau, indkomst og fuldtids-/deltidsansættelse samt andelen af henvisninger til social pleje som praktisk hjælp, personlig hjælp og motion. Grupperne blev sammenlignet med anvendelse af chi-square-, Wilcoxon-Mann Whitney- eller Kruskal Wallis-test efter behov.

RESULTATER: Studiepopulationen bestod af 8.336 patienter med MS og 83.360 matchede individer. Gennemsnitsalderen var 63,3 år (SD: 8,9), og 68,2% var kvinder. Blandt patienterne med MS var fordelingen af fænotyper 44,0% RRMS, 25,5% SPMS, 16,7% PPMS og 13,8% uklassificerede. MS-befolkningen modtog signifikant mere social pleje med en median på 20,5 (Q1-Q3: 5,0-60,5) timers praktisk

hjælp og 2,0 (Q1-Q3: 1,3-4,1) timers personlig pleje hver måned ($P < .0001$). I aldersgruppen 50-65 år var andelen af patienter med MS, der modtog førtidspension, markant højere end baggrundsbefolkningen (46,1% versus 13,3%, $P < .0001$), og for dem, der havde et job, var årslønnen væsentligt lavere (45.000€ versus 50.000 €, $P < .0001$).

DISKUSSION: Den aldrende befolkning med MS modtager mere social pleje og klarer sig betydeligt dårligere på socioøkonomiske parametre sammenlignet med baggrundsbefolkningen. Denne viden giver behandlere og beslutningstagere mulighed for at medtage disse særlige udfordringer i deres fremadrettede planlægning af tiltag for denne patientgruppe.

Diskontinuationsrater under behandling med dimethyl fumarat hos patienter med multipel sklerose – et nationalt kohortestudie

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HYPOTESE: Forudsætningen for at opnå effekt fra et lægemiddel afkræver at det administreres korrekt og indtages med en korrekt frekvens.

Tidligere studier har vist at non-adherence ved multipel sklerose er associeret med øget sygdomsaktivitet, lavere livskvalitet og højere sundhedsudgifter.

METODE: Data blev indsamlet via det Danske Skleroseregister i samarbejde med Dansk Multipel Sklerose Gruppe og inkluderende data fra alle patienter der er behandlet med dimethyl fumarat (DMF) i Danmark. Standard residualer blev beregnet til at sammenligne skleroseklinikker og årsager til behandlingsophør. Survival analyse blev foretaget for at sammenligne discontinuations rater og årsag til behandlingsophør med log-rank test cox proportional hazards og Kaplan-Meier plots.

RESULTATER: Studiet inkluderede 2.448 patienter der blev behandlet i perioden 2013–2020 i 13 danske skleroseklinikker. Den gennemsnitlige behandlingsperiode var 26 måneder (=5.382 behandlingsår). 49% gennemførte behandling med DMF uden behandlingsophør. Årsagerne til behandlingsophør var følgende: Bivirkninger (54.5%, n=656), sygdomsaktivitet (26.1%, n=315), graviditet (9.4%, n=113) or andre årsager (10.0%, n=159). Ved sammenligning af standard residualer var der signifikant forskel imellem skleroseklinikkerne på diskontinuationsrater på grund af bivirkninger, herunder gastrointestinale bivirkninger, flushing og lymfopeni. Behandlingsophør på grund af bivirkninger var hyppigere hos kvinder end hos mænd både grundet lymfopeni (p=0.04) og flushing (p=0.04), men ikke på grund af gastrointestinale bivirkninger (p=0.07).

DISKUSSION: Dette nationale registerstudie demonstrerer forskelle på diskontinuationsrater og årsager til behandlingsophør imellem danske skleroseklinikker. Årsagen hertil kan være betinget af de behandlingstilbud som patienterne møder lokalt. Der er behov for yderligere studier der undersøger hvorfor der er forskel på diskontinuationsrater og årsager til behandlingsophør.

Expression of Bruton's tyrosine kinase in brain of MS patients and during experimental demyelination

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HYPOTHESIS: Inhibition of Bruton's tyrosine kinase (BTKi) is a promising novel therapy of MS and examined in phase 3 clinical trials. BTK inhibitors can cross the blood-brain barrier and interact with progressive tissue damage manifesting clinically as smoldering MS. To predict the potential long-term effect of BTKi on such progressive pathology, we examined BTK expression in different MS brain lesions, resident cells of the brain, and in a degenerative MS model associated with microglia activation in vivo.

METHODS: We used next-generation RNA sequencing to examine BTK expression in postmortem 25 control WM and 73 MS tissues (19 NAWM, 6 remyelinating, 18 active, 13 inactive and 17 chronic active lesions). Presence of CD20⁺ B cells and MHCII⁺ microglia were examined by immunohistochemistry. We applied quantitative PCR (QPCR) to examine BTK expression in the mouse brain during experimental de- and remyelination in the cuprizone model, and in microglia, astrocytes, neurons, oligodendrocyte precursors, and immature oligodendrocytes isolated by microbead kits. Differentially expressed genes were identified by generalized linear model corrected for age and sex and filtering by Benjamini-Hochberg. Expression level of BTK was analyzed by one-way ANOVA corrected for multiple comparisons. BTK expression during de- and remyelination was compared to con-

trols using an unpaired two-tailed t-test. Statistical significance was set at FDR/ $p < 0.05$.

RESULTS: BTK expression was significantly increased in active and chronic active lesions. The active lesions contained a high number of perivascular B cells besides microglia/macrophages. Chronic active lesions were characterized by presence of microglia in the rim. Increasing BTK expression was found during cuprizone-induced de- and remyelination in the mouse brain. Microglia expressed BTK at a very high level (120-fold), while BTK expression in the other cell types was marginal (2–4-fold).

DISCUSSION: By reducing BTK expression, BTKi will exert effect on B cells, macrophages, and microglia in active lesions. BTKi will also limit microglia activation in the rim of chronic active lesions, where chronic tissue damage propagates. Therefore, BTK inhibition in the CNS will target both the acute and progressive pathology of smoldering MS. CNS effects will also complement BTK inhibition of B cells and macrophages in the peripheral compartment.

Rygestatus i relation til væske-biomarkører hos patienter med akut synsnervebetændelse

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HYPOTESE: Rygning er associeret med accelereret progression ved multipel sclerose (MS). Da der ikke ses forskelle i sygdomsprogression mellem aldrig rygere og tidligere rygere, tyder det på, at effekten af rygning er reversibel og kausal. Hypotesen er, at sammenligninger på tværs af patientgrupper med forskellig rygestatus kan bruges som model til at identificere mekanismer, der driver sygdomsprogression ved MS.

METODER: Data om rygestatus (daglig ryger, lejlighedsryger, tidligere ryger, aldrig ryger) blev indhentet via spørgeskemaundersøgelse blandt patienter med akut synsnervebetændelse (ON), som fik udført lumbalpunktur i forbindelse med udredning for MS i årene 2018-2021. Celletal i cerebrospinalvæsken (CSF), IgG-index, Qalb (albuminkvotienten mellem CSF og serum) og serum vitamin-D blev sammenlignet mellem daglige rygere, aldrig rygere og tidligere rygere.

RESULTATER: Der blev rekrutteret 75 ON patienter (65% kvinder, alder: (median=32, IQR=(27-40)), 61% fik MS-diagnosen) med følgende fordeling blandt rygestatusgrupperne: 36 aldrig rygere, 19 daglige rygere, 5 lejlighedsrygere og 15 tidligere rygere. Vi fandt ingen forskelle i celletal i CSF og IgG-index mellem grupperne. Daglige rygere havde højere Qalb sammenlignet med aldrig rygere ($p=0.005$), og tidligere rygere ($p=0.03$). Vi fandt ingen forskel i Qalb mellem aldrig rygere og tidligere rygere ($p=0.96$). Daglige rygere havde ligeledes markant lavere IgG

i serum sammenlignet med aldrig rygere ($p=0.00002$), men ikke sammenlignet med tidligere rygere ($p=0.09$). Forskellen i serum IgG mellem tidligere rygere og aldrig rygere var ikke signifikant ($p=0.058$). Daglige rygere havde signifikant lavere serum vitamin-D sammenlignet med aldrig rygere ($p=0.029$) og tidligere rygere ($p=0.024$). Vi fandt ingen forskel i serum vitamin-D mellem tidligere rygere og aldrig rygere ($p=0.41$). Effekterne af rygning på Qalb, serum IgG og serum vitamin-D var fortsat signifikante efter justering for MS-diagnose, alder og køn. Modellerne afslørede ligeledes en sammenhæng mellem alder og Qalb, samt diagnosticering med MS og serum vitamin-D.

DISKUSSION: Ovenstående data understøtter en effekt af rygning på permeabiliteten mellem blod og CSF, systemisk humoral immunitet og niveauerne af vitamin-D i serum. Det tyder på, at Qalb normaliseres hurtigere end serum IgG efter rygeophør. Fremtidige studier bør undersøge sammenhængen mellem de fremlagte mekanismer og sygdomsprogression ved MS.

Udfordringer ved estimering af effekten af sygdoms-modificerende behandling ved MS i åbne observationsstudier.

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HYPOTESE: Korttidsprognosen ved atakvis MS er i DK blevet bedre i senere debut-kohorter siden 1996, hvor 'disease modifying therapy' (DMT) blev tilgængelig. En sandsynlig årsag er, at patienter fra nyere debutkohorter kommer tidligere i behandling og hyppigere eskalere til høj-effektive DMT. Åbne ikke-randomiserede behandlingsstudier påvirkes af selektions-bias og bias fra ukendte eller umålte 'confoundere' og har derfor udfordringer ved at dokumentere virkningen. Formålet med denne undersøgelse er at analysere behandlingseffekt ud fra den komplette opfølgning i Det Danske Scleroseregister og at korrigere for de nævnte bias med nye epidemiologiske teknikker med brug af 'Instrumental Variable' ('IV').

METODER: 6014 patienter fra Det Danske Scleroseregister med debut af atakvis MS i årene 1996 til 2010 blev fulgt fra debut indtil bekræftet forekomst af EDSS-4 og EDSS-6, 'drop-out' eller til censurering 12 år efter debut. Vi definerede behandlings-indeks som $(10 \times \text{antal år under høj-effektiv DMT} + 0,5 \times \text{antal år under moderat effektivitet DMT})/\text{observationstiden}$. En 'IV' er en ekstern variabel, der er kausalt forbundet med eksponeringen (her: behandling), men ikke med resultatet, kun indirekte gennem behandling eller ved selektion. Som 'IV' brugte vi debut-kohorte delt i 3 (1:1996-2000; 2:2001-2005; 3:2006-2010). Cox regression med og uden 'G-estimering' med 'IV' blev anvendt til analysen af tid til EDSS-4 og -6. Ved 'G-estimering' dannes for hver patient et hypotetisk ubehandlet udfald, som indgår i Cox-regressionen.

RESULTATER: Pga. 'confounding' viste en køns- og alders-justeret Cox regression en tilsyneladende skadelig virkning af behandlingen, idet kumuleret risiko for EDSS-4 og EDSS-6 blev øget med hhv. 11% og 18% for hver enheds øgning af behandlings-indeks. Efter inklusion af kohorte med 'G-estimering' vendte sammenhængen og viste nu en klar og statistisk signifikant gavnlig effekt af behandling, idet den kumulerede risiko for EDSS-4 og EDSS-6 blev reduceret med hhv. ca. 27 % og 25% for hver enheds øgning af behandlings-indeks.

DISKUSSION: Undersøgelsen bekræfter, at DMT effektivt forsinket udviklingen af blivende handicap ved atakvis MS og at vurdering af behandlingseffekt i observationsstudier er mulig med nye epidemiologiske metoder, der korrigerer for ukendte eller umålte 'confoundere'.

Higher disability status is associated with substantial negative alterations of physical activity levels in persons with multiple sclerosis

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HYPOTHESIS: Whilst physical activity (PA) is highly potent in eliciting multiple health benefits, evidence shows that persons with multiple sclerosis (pwMS) have different PA levels than healthy controls. However, limited knowledge exists on the differences in PA levels across disability status in pwMS. Therefore, the purpose of this study was to determine PA levels according to EDSS scores of pwMS compared to healthy controls (HC).

METHODS: 137 pwMS (73% females), age 41±13 years, EDSS 2.5±1.7, time since diagnosis (tsd) 4.3±6.6 years; 101 HC (67 % females, age 41±13 years). PA was assessed by 7-day thigh-worn accelerometry, with PA data being analyzed during awake time (pwMS 13.9±1.0; HC 13.9±0.8). PA outcomes comprised counts per minute (CPM) per day as well as time spent in sedentary (min), light (min), moderate (min) and vigorous (min) per day. EDSS groups were divided into four groups: MS_{EDSS}^{0-1.5}, MS_{EDSS}^{2-2.5}, MS_{EDSS}^{3-4.5}, and MS_{EDSS}^{5-6.5}. Comparison of PA levels across groups (HC and MS groups, respectively) were carried out using linear mixed model in STATA 17.

RESULTS: PA differed markedly ($p < 0.001$) between HC and pwMS for CPM (807±294 vs. 579±275), sedentary (562±61 vs. 591±69 min), light (225±56 vs. 210±59 min), moderate (38.8±20.7 vs. 26.8±20.3 min) and vigorous (6.3±1.0 vs. 1.2±0.2 min). Further differences were revealed across the 4 EDSS groups for CPM (680±315 ≈ 628±212 ≈ 577±248 > 287±174), sedentary (581±70 ≈ 576±63 ≈ 591±62 <

649±59 min), light (207±51 > 238±49 < 505±60 > 171±64 min), moderate (30.6±19.8 ≈ 28.3±15.4 ≈ 31.2±26.3 > 8.2±9.3 min) and vigorous (1.8 [0.3:10.0] ≈ 2.0 [0.4:6.4] ≈ 1.2 [0.6:3.1] > 0.2 [0.02:1.4] min).

DISCUSSION: Overall, PA levels differed markedly between pwMS and HC. Moreover, disability status was associated with PA levels in pwMS. This was specifically accentuated in pwMS having more severe disability status (i.e., MS_{EDSS}^{5-6.5}), shown to be more sedentary along with having lower light, moderate, and vigorous PA compared to no disability, mild and moderate disability status (MS_{EDSS}^{0-1.5}, MS_{EDSS}^{2-2.5}, MS_{EDSS}^{3-4.5}, respectively). Considering the well-known beneficial effects of PA, these findings emphasize the importance of initiatives to facilitate physical activity engagement in pwMS, especially for those with severe disability status.

New enhancing MRI lesions associate with IL-17, neutrophil degranulation and integrin microparticles: multi-omics combined with frequent MRI

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HYPOTHESIS: To identify early markers related to blood-brain barrier disruption as initial event for lesion evolution, we combined frequent MRI with plasma multi-omics.

METHODS: Five patients with RRMS without disease-modifying treatment underwent weekly MRI with gadolinium for 8 weeks for extensive monitoring of active lesions. Plasma samples (n=40) taken at each measurement were analyzed for protein biomarkers

of inflammation by quantitative proteomics, for cytokines using multiplex immunoassays, and for soluble secreted endothelial extracellular vesicles (EVs) by an optimized endothelial stress EV Array.

RESULTS: The proteomics analysis of plasma from the untreated RRMS patients yielded quantitative information of 208 proteins at each patient time point (n=40). This identified distinct patient profiles reflecting the overall MRI data. Principal component analysis indicated the individuality of plasma profiles in patients correlated to MRI activity level and individual plasma profiles. IL-17 was up-regulated at all time points during 8 weeks in patients with high vs low MRI activity. Hierarchical clustering indicated that the number of new FLAIR lesions, new gadolinium (Gd) enhancing lesions, the total number of Gd lesions and the number of lesions with maximum Gd intensity clustered together with IL-17, and with IL-12p70 and IL-1b. The same MRI outcomes also showed clustering with EV markers CD62E/P, MIC A/B, ICAM-1, CD42A. All four MRI outcomes correlated positively with levels of IL-17 and EV-ICAM-1. IL-1b levels positively correlated with the number of new Gd-enhancing lesions, new FLAIR lesions and total number of Gd-enhancing lesions. IL-6 levels positively correlated with the number of new FLAIR lesions. Random Forests and linear mixed models identified IL-17, CCL17/TARC, CCL3/MIP-1a and TNF- α as composite biomarkers associated with new lesion evolution.

DISCUSSION: Systemic IL-17 and related cytokines are important in blood-brain barrier disruption and initiating acute brain inflammation in MS similarly to experimental models. This may suggest that IL-17 antagonization may prevent lesion evolution in MS. Abundant protein changes comparing MRI activity groups included acute phase proteins, complement proteins and components of neutrophil degranulation indicating the role of the innate immune system as well.

Substantial deficits and differences exist across measures of walking capacity in patients with multiple sclerosis

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HYPOTHESIS: Walking capacity as well as walking ability are substantially impaired in persons with multiple sclerosis (pwMS). Therefore, assessment and continuous monitoring of walking performance is important to both patients, clinical practice and research. However, since walking is a complex construct, a numerous outcome measures on walking exist and thus captures different aspects of walking deficits. Hence, the objective of this study was to evaluate deficits and diversities between three frequently applied walking capacity outcomes in pwMS compared to healthy controls (HC).

METHODS: In a large cohort of pwMS, walking capacity was assessed 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). Data were compared to available normative reference data in HC. Furthermore, perceived walking ability was assessed using the 12-item-MS-walking-scale (MSWS).

RESULTS: A total of 241 pwMS (68% females) were involved in the study (age: 57.8±11.6 yrs [range 26–81 yrs], patient determined disease steps (PDDS) 3.0±1.9 [range 0–7]), time since diagnosis 12.5±9.7 yrs [range 0–49 yrs]), type of MS: relapse remitting; n=138, secondary progressive; n=37, primary progressive; n=44, unknown; n=21). Results for the T25FWT, 6MWT and SSST were 1.37±10.5 m/s (n=227), 416±163m (n=219) and 0.107±0.537 rounds/sec (n=223), respectively. Walking ability in terms of the MSWS was 33.1±2.8 (n=222). Compared

to normative reference data in HC, deficits were observed across all walking capacity outcomes (p<0.001), corresponding to: T25FWT -26[-30;-23]%, 6MWT -36[-39;-32]% and SSST -44 [-47;-40]%. Deficits differed across walking capacity outcomes (p<0.001), corresponding to: T25FWT vs. 6MWT -10[-15;-4]%, T25FWT vs. SSST -17[-22;-12]%, 6MWT vs. SSST -8[-13;-2]%.

DISCUSSION: Compared to reference-data from HC, substantial deficits were observed in pwMS for all walking capacity outcomes. Specifically, SSST, encompassing balance and coordination during walking, was shown to be superior in capturing walking capacity impairments compared to measures on walking endurance (6MWT) and especially walking speed (T25FWT). Altogether, clinicians should either consider using the SSST as a “stand-alone” measurement of walking capacity or ideally apply a range of walking capacity and ability measures, as shown here, to better capture the multiple dimensions of walking impairments in pwMS.

Abstracts



Videnskabelige poster

Sakral nervemodulation til patienter med multipel sclerose (MS) med gener fra blære, tarm og den seksuelle funktion

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HYPOTESE: Efter mere end 10 år med MS har næsten 100% af MS-patienter problemer med vandladningen. En stor andel har også problemer med afføringen og den seksuelle funktion. Sakral nervemodulation (SNM) er en behandling, der er godkendt til patienter uden neurologisk sygdom, som har problemer med vandladningen og afføringen. Vi antager, at SNM kan forbedre MS-patienters livskvalitet ved at behandle deres vandladningsgener og at effekten er superior til nuværende standard behandling heraf. Formålet med studiet er at undersøge effekten af SNM på patienter med MS, som har problemer med vandladningen, afføringen og den seksuelle funktion og sammenligne det med standard behandling heraf.

METODE: Et randomiseret internationalt multicenter studie med inklusion af 60 patienter. Patienter randomiseres ikke-blindet 1:1 mellem standard behandling og standard behandling plus SNM. Patienterne følges med væskevandladningsskemaer og relevante spørgeskemaer. Komplikationer og implantationskarakteristika monitoreres.

RESULTATER: I juni 2023 afslutter pilotstudiet, hvor 14 patienter er inkluderet. 11 patienter er responders til SNM med > 50% bedring af vandladningssymptomerne. Det randomiserede studie starter august 2023.

DISKUSSION: Der foreligger endnu ikke data til diskussion og endelig konklusion.

Elevated EBNA1 Antibodies Found in Multiple Sclerosis Patients Compared to Healthy Controls

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HYPOTHESIS: Multiple sclerosis (MS) is a chronic demyelinating disease of the central nervous system. There is an increased intrathecal antibody synthesis in MS patients, which could be caused by increased viral activity. The role of Epstein-Barr virus in MS is a hot topic. Could quantification of antibodies to Epstein-Barr Virus antigen EBNA1-full length (EBNA1-FL) be used to discriminate between MS patients and healthy controls?

METHODS: Specific IgG concentrations against EBNA1-FL in paired CSF and serum samples were examined by direct enzyme-linked immunosorbent assays. Samples were from 78 patients with MS from Rigshospitalet and 15 healthy controls.

RESULTS: Significantly elevated responses were recorded in patients with MS compared to healthy controls. CSF analyses were not more sensitive than serum analyses. Higher sensitivity or specificity was not obtained when normalizing to total albumin concentration or total IgG concentration.

DISCUSSION: Antibody levels against EBNA1 can be used to discriminate between HCs and MS patients depending on the type of antigen and interindividual variances in antibody productions.

Cognitive impairment in primary progressive multiple sclerosis: a matter of grey matter nuclei, cortical grey matter, white matter, or lesion damage?

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HYPOTHESIS: Deep grey matter nuclei damage contributes to cognitive impairment in primary progressive multiple sclerosis (PPMS). The aim is to evaluate the extent of involvement of damage in the deep grey matter nuclei to cognitive impairment and additionally the influence of alterations in cortical grey matter (CGM), normal-appearing white matter (NAWM), and lesions.

METHODS: In 60 PPMS patients, we applied cognitive tests (n =3) and acquired brain MRI (3 Tesla). Data stem from a placebo-controlled, double-blinded treatment trial. Regional MRI included CGM, thalamus, putamen, accumbens, caudate nucleus, hippocampus, globus pallidum, NAWM, and lesions. MRI modalities for all regions were volume, mean diffusivity (MD), magnetization transfer ratio (MTR), and fractional anisotropy (NAWM and lesions only). Statistical analyses included linear regression in 2 steps adjusted for age, sex, disease duration, and years of education. Variance inflation factor analyses revealed no collinearity. Level of significance was set at $p < 0.0006$ in the step 1 analyses (Bonferroni corrected) and $p < 0.05$ in step 2.

RESULTS: Step 1 analyses: Symbol Digit Modalities Test (SDMT) was associated with damage in three deep grey matter nuclei: thalamus, accumbens, and hippocampus. California Verbal Learning Test 2 (CVLT-II) was associated with two deep grey matter nuclei: accumbens and globus pallidum. Brief Visuospatial Memory Test-Revised (BVMT-R) was associated with two deep grey matter nuclei: accumbens and caudate nuclei. Step 2 analyses: Lesion volume was an independent explaining factor for impairment on SDMT and CVLT-II, and alterations in MD in hippocampus independently explained reduced test scores on SDMT alongside volume of NAWM. Volume of accumbens was an independently explaining factor of impairment of CVLT-II. For BVMT-R, altered MTR in CGM and volume of caudate nucleus were independently explaining the reduction in performance.

DISCUSSION: Cognitive impairment was associated with damage in deep grey matter nuclei that are part of the monoaminergic pathways, the basal ganglia, and the limbic system. Additionally, cognitive impairment was associated with alterations in CGM, NAWM, and lesions, indicating diffuse and complex pathogenetic contributions to cognitive impairment in PPMS supported by histopathology studies.

Modulering af den mikrogliale TNF-produktion ved ikke-kodende RNA i T celle-infiltrerede MS læsioner

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HYPOTESE: Den mikrogliale produktion af tumor nekrose faktor (TNF) reguleres i T celle-infiltrerede multipel sklerose (MS)-læsioner af Th1-cytokinet interferon gamma (IFN- γ) via regulatoriske, ikke-kodende RNA-molekyler.

METODER: Med baggrund i studier udført på en musemodel for MS samt på IFN- γ -stimulerede primære, murine mikroglia, har vi selekteret – via sekventering og bioinformatik – en gruppe af ikke-kodende RNA med formodet regulatorisk effekt på den mikrogliale TNF produktion. Som i vores musemodel, anvendes nu in situ hybridisering (ISH) for at undersøge disses ekspresion i vævsprøver fra afdøde patienter med MS med aktive eller inaktive læsioner samt i 'normal-appearing' hvid substans (n=10/ gruppe). Det paraffinindstøbte og friskfrosne væv er blevet eller vil blive karakteriseret vha. immunhistokemiske teknikker og qPCR og analyseret for bl.a. CD68, CD3, MBP, CD11b, TNF og IFN- γ . Ved brug af RNAscope teknologi, som kombinerer ISH med immunhistokemi, vil vi ydermere undersøge, om TNF co-lokaliserer med de ikke-kodende RNA i mikroglia. For at undersøge funktionen af de ikke-kodende RNA, har vi behandlet IFN- γ - og vehikel-stimulerede primære mikroglia med nanopartikler indeholdende identiske eller komplementære sekvenser af de ik-

ke-kodende RNA. Niveauet af TNF mRNA og protein er blevet analyseret med hhv. qPCR og ELISA.

RESULTATER: I vores musestudier fandt vi, at IFN- γ havde betydelig indflydelse på det mikrogliale transkriptom inklusiv TNF mRNA og 6 selekterede, ikke-kodende RNA molekyler relateret til TNF. To af disse, som var signifikant nedreguleret, kan potentielt targetere TNF mRNA og dermed regulere den mikrogliale produktion af TNF protein direkte. Kvantitative analyser på musevæv har ydermere vist, at udtrykket af ikke-kodende RNA korrelerer med ekspresionen af TNF mRNA og protein, CD11b immunreaktivitet, samt infiltration af IFN- γ -mRNA-udtrykkende T celler. Kvantitative analyser på humant væv er igangværende.

DISKUSSION: Ikke-kodende RNA udtrykkes af flere celletyper i hjernen, og brug af ISH alene kan intet sige om reguleringen specifikt i mikroglia. Derfor er de forestående co-lokalisationsstudier vigtige, da vi her kan undersøge, om netop de TNF-udtrykkende mikroglia udtrykker de selekterede ikke-kodende RNA. Vores formodning er, at de TNF-targeterende ikke-kodende RNA ikke ses co-udtrykt i TNF-producerende mikroglia. Projektets resultater vil potentielt kunne bane vejen for ny medicin, hvor den kliniske effekt opnås ved modulering af TNF-udtrykket.

Modeling PMS-like cortical pathology in mouse

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HYPOTHESIS: Multiple sclerosis (MS) is the most common demyelinating disease of the central nervous system (CNS) in young adults. MS is believed to have an autoimmune etiology. Subpial cortical lesions and grey matter pathology are major hallmarks of progressive MS (PMS). To date, there are very few approved therapies for PMS, and they are most effective at the disease stage associated with inflammation. An intact blood-brain barrier (BBB) that restricts access to lesions is a further hindrance. The goal of our research is to establish an animal model which would enable therapeutic developments. PMS-characteristic subpial cortical pathology is not well-modelled by EAE, the most commonly-used animal model for MS. Our aim is to create meningeal inflammation, cortical inflammation with activated microglia/macrophages and understand the role of microglia in the lesion and its interaction with other immune cells involved.

METHODS: Mice were fed with 0.3% cuprizone for 6 weeks. We delivered cytokines by focal injection to subarachnoid space, followed by intrathecal injection of microglia primed in a neurodegenerative environment in the 5th week. After completion of their diet plan the mice were sacrificed and the brains were processed for immunohistochemistry. As an alternative approach, we induced focal laser-induced injury for localization of cortical lesions. We surgically thinned the skull and used a two-photon laser to induce a focal burn injury in the cortex.

RESULTS: We induced cortical inflammation by feeding the myelin toxin cuprizone to mice. With superimposition of subarachnoid injection of pro-inflammatory cytokines and intrathecal injection of primed microglia, we induced subpial cortical demyelination with intense microglial and astroglial response in the region. Similar focal subpial microglial activation was induced by laser irradiation. This was intensified by addition of a viral vector expressing IFN- γ . Preliminary results showed presence of monocytes and CD11c+ microglia in the irradiated region.

DISCUSSION: We will further optimize and establish these animal models that mimic the hallmark pathology of PMS and investigate the underlying pathological mechanism. We are applying candidate therapeutics for the amelioration of PMS-like pathology induced in these animal models. This will improve our understanding of, and lead to better treatment of PMS.

Betydningen af ferroxidasen ceruloplasmin for remyelinisering og mikroglia aktivitet i cuprizon-behandlede mus

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HYPOTESE: Ferroxidasen ceruloplasmin har betydning for remyeliniseringen undersøgt ved brug af cuprizon-modellen for de- og remyelinisering.

METODER: Ceruloplasmin (Cp) knockout mus (B6N(Cg)-Cptm1b(KOMP)Wtsi) blev behandlet med cuprizon (CPZ) holdigt foder i 6 uger, efterfulgt af 2 uger på normalt foder, for at undersøge remyeliniseringen. De eksperimentelle grupper i studiet består af naïve, demyeliniserede (6 uger, DEM) og tidligt remyeliniserede (6+2 uger REM) mus. Musene var 4-5 mdr. gamle ved CPZ-behandlingens afslutning. Hjernebarken blev udtaget, frosset og skåret i vævssnit, som blev farvet med luxol fast blue (LFB) kontrasteret med cresyl violet til visualisering af myelin og cellekerner. Mikroglia-celle-reaktionen blev undersøgt ved brug af en CD11b immunhistokemisk farvning. Både LFB og CD11b farvningerne blev analyseret i corpus callosum (CC) ved intensitetsmålinger. Yderligere blev systematisk opsamlede vævssnit også anvendt til kvantitativ PCR for at undersøge effekten af Cp på oligodendrocytlinje-markører og gener involveret i jernmetabolismen.

RESULTATER: Resultaterne viser at både homo- og heterozygote Cp knockout mus udvikler normalt myelin under udviklingen og at begge typer knockout mus fremviser en signifikant mangel på myelin i CC efter 6 ugers CPZ-behandling. Det samme er gældende for vildtype mus. Cp knockout mus har en lavere kernefraktion i CC undersøgt med cresyl violet, samt et lavere udtryk af CD11b efter 6 ugers CPZ-behandling sammenlignet med vildtype mus. Korrelationsanalyse af gen-ekspressions-data tyder på en sammenhæng mellem niveauerne af Cp, PDGFRa, CD11b og GFAP mRNA.

DISKUSSION: Sammenlagt tyder vores resultater på at Cp ikke påvirker demyeliniseringen eller den tidlige remyelinisering i unge voksne mus. Derimod tyder data for CD11b farvningen og kernefraktionen på at Cp har betydning for de cellulære reaktioner, herunder mikroglia-celle-aktivering, i CC under CPZ-behandling. Dette kan have betydning for både de- og remyeliniseringen. Det vil være interessant at undersøge om studiet ville få et antal udfald hvis det udføres i ældre mus. Det er desuden velkendt at CPZ-modellen ikke indeholder store mængder af T-celler. Det vil derfor kunne være interessant at undersøge, hvad der sker med demyeliniseringen og nydannelsen af oligodendrocytter i en kombineret model med CPZ og immunisering.

Muskelstyrke og fysisk funktion hos ældre personer med multipel sklerose – afdækning af forskelle i forhold til matchede raske kontrolpersoner

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HYPOTESE: Der er begrænset viden om funktionsevnen hos ældre personer med multipel sklerose (MS). Nærværende studie har derfor til formål at undersøge forskelle i neuromuskulær funktion, fysisk funktion, kognitiv funktion og kropskomposition mellem ældre personer med multipel sklerose (MS) og matchede raske kontrolpersoner (HC). Det forventes, at MS har reduceret neuromuskulær funktion, fysisk funktion og kognitiv funktion sammenlignet med HC.

METODER: Deltagende MS-patienter i dette studie er alle deltagere i et randomiseret kontrolleret studie, som har til formål at undersøge effekterne af 24-ugers power-træning. Forsøgspersonerne er alle over 60 år og har en EDSS fra 0-6,5. Nærværende substudie er et tværsnitsstudie som alene indeholder data fra baseline tests af MS-patienter fra nævnte RCT-studie. De samme tests er udført på alders- og køns-matchede HC. Data indsamles i øjeblikket men forventes at omfatte 27 MS-patienter samt 16 HC når DAREMUS konferencen afvikles. Alle deltagere får målt neuromuskulær funktion i et isokinetisk dynamometer med MVC og rate of force development (RFD) som udfald. Fysisk funktion måles ved 6MWT med distance som udfald, samt 25 fods gangtest (25FWT), 6 spot steptest (6SST) og 9 step stair ascent (9SSA) med tid som udfald. Kognitiv funktion evalueres ved selective reminding test og simple digit modalities test. Data i forbindelse med kropskomposition indsamles via DXA-scanning.

RESULTATER: Da data pt. er under indsamling, er data endnu ikke opgjort. Ved DAREMUS mødet 2023 vil der forventeligt kunne

præsenteres data på 27 ældre personer med MS samt et tilsvarende antal HC.

DISKUSSION: På trods af, at cirka 1/3 af alle MS-patienter er over 60 år gamle, er det begrænset, hvad der findes af forskning på denne population. Der findes flere ligheder mellem de degenerative processer, som MS og alderdom medfører. Hvor den "kombinerede konsekvens" af aldring og MS antageligt medfører markant forøgede problemer. Sidstnævnte omfatter bl.a. nedsat muskelmasse, muskelstyrke, fysisk funktion og kognitiv funktion. Kortlægning af evt. forskelle vil kunne sikre et bedre grundlag for at planlægge effektiv træning til gruppen af ældre MS-patienter. Dette studie vil derfor kunne fungere som udgangspunkt for bedre målretning af fremtidige longitudinelle træningsstudier for ældre personer med MS.

Microfibrillar-associated Protein 4 as Potential Marker of Acute Relapse in Inflammatory Demyelinating Diseases of the CNS: Clinical Aspects

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HYPOTHESIS: Microfibrillar-associated protein 4 (MFAP4) is an integrin ligand expressed in the vascular extracellular matrix. Integrins are implicated in vascular leakage. We hypothesized that MFAP4 levels act as a biomarker for disease activity in inflammatory demyelinating diseases of the central nervous system.

METHODS: This cross-sectional multicenter study involved 152 patients (49 MS, 62 aquaporin-4-IgG positive neuromyelitis optica spectrum disorder, 22 myelin oligodendrocyte glycoprotein associated disease (MOGAD), and 19 isolated optic neuritis (ION)) recruited from eight different institutions across six countries. We measured MFAP4 levels in cerebrospinal fluid (CSF) and serum, using an AlphaLISA assay.

RESULTS: CSF MFAP4 levels were reduced in patients during acute attacks compared to healthy controls (HC). There was a positive correlation between the number of relapses and CSF MFAP4 levels ($\rho=0.33$, $p=0.004$). CSF MFAP4 levels were lower in 53 samples obtained at presenting attack (mean U/mL: 14.3, MOGAD 9.7, and ION 14.6 relative to HC 17.9. ($p=0.013$, $p=0.000$ and $p=0.019$, respectively). All patients with acute ON relapse ($n=68$) had reduced CSF MFAP4 relative to HC (mean U/mL: 14.5 vs. 17.9, $p=0.006$). CSF MFAP4 levels correlated negatively with relapse severity ($\rho=-0.41$, $p=0.017$).

DISCUSSION: Our findings suggest a potential role for MFAP4 as a biomarker for disease activity and relapse severity in patients with IDD. The data underscore the role of the timepoint of MFAP4 determinations relative to an attack.

Molekylær og cellulær effekt af B-celle-fjernelse hos patienter med aktiv multipel sklerose inkluderet i DanNORMS.

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HYPOTESE: Terapeutisk fjernelse af perifere B-celler med anti-CD20-monoklonale antistoffer har vist sig som værende en høj effektiv behandling mod multipel sklerose (MS). Dog er behandlingens effekt på andre immunceller samt dens virkningsmekanisme hos MS-patienter stadig uklar. Vores hypotese er, at fjernelse af B-celler fra periferien giver både akutte og langvarige ændringer på de andre perifere immunceller på et cellulært og molekylært niveau. En undersøgelse af disse ændringer vil hjælpe os med at forstå anti-CD20-behandlingens virkningsmekanismer i MS-patienter, og resultaterne vil blive relateret til de kliniske resultater fra det kliniske fase 3 studie, DanNORMS.

METODER: Vi har isoleret immunceller fra blod af MS-patienter før og under deres anti-CD20-behandling på forskellige tidspunkter. Vi har udført flerfarvet flow-cytometri (FACS) til at undersøge de cellulære og molekylære ændringer, som forekommer i løbet af behandlingen. Yderligere har vi inkluderet raske kontroller for at sammenligne sammensætningen af immunceller med MS-patienter fra før de startede i behandlingen.

RESULTATER: Med vores FACS-resultater ser vi en klar separation af forskellige populationer og subpopulationer af immunceller. Vi har med vores FACS-panel separeret monocytter, B-, T- og NK-celler fra hinanden og yderligere adskilt subpopulationer af T- og NK-celler fra hinanden.

DISKUSSION: I vores forsøg har vi brugt flerfarvet flow-cytometri til at identificere forskellige immunceller i blodet fra MS-patienter baseret på specifikke overflademærker, der er karakteristiske for de enkelte celletyper. Vi ser med vores FACS-panel en tydelig separation af immuncellepopulatio-

nerne samt en dybere separering af subpopulationerne. Vi har på nuværende tidspunkt analyseret nogle FACS-resultater fra et par patientprøver, hvor en mere detaljeret analyse er undervejs og klar til DAREMUS Nationalt Forskningsmøde. Der ønskes på sigt en sammenhæng mellem vores cellulære resultater og de kliniske resultater fra DanNORMS. Derudover vil vi associere vores FACS-resultater med vores igangværende single-celle RNA-sekventeringsdata fra samme patientprøver.

Comprehensive evaluation of self-management skills following multidisciplinary rehabilitation in persons with MS – The Danish MS Hospitals Rehab Study

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HYPOTHESIS: Health education is often an integral part of rehabilitation programs for persons with multiple sclerosis (pwMS), aiming to promote self-management behavioral changes and skills. One tool that can be used to comprehensively evaluate this is the Health Education Impact Questionnaire (heiQ; 40 questions), measuring 8 different constructs. However, few (if any) randomized controlled trials have evaluated the effects of personalized multidisciplinary rehabilitation (MDR) on heiQ in pwMS. We hypothesize that 4 weeks of inpatient MDR will have a beneficial impact on heiQ in pwMS.

METHODS: A total of n=405 pwMS were enrolled in the study, and evenly randomized into 4 weeks of MDR or wait-list control. All pwMS filled out the heiQ questionnaire at baseline and after 2 as well as 12 months of follow-up. The heiQ comprise 8 different constructs (1–4 point scale): health-directed activities (HDA), positive and active engagement in life (PAEL), emotional distress (ED), self-monitoring and insight (SMI), constructive attitudes and approaches (CAA), skill and technique acquisition (STA), social integration and support (SIS), health services navigation (HSN).

RESULTS: Substantial improvements (between-group difference (mean diff [95%CI]) + effect size (ES)) were observed at 2 months follow-up for HDA (0.32[0.25:0.39], ES=0.51), PAEL (0.08 [0.03:0.13], ES=0.15), SMI (0.15 [0.11:0.20], ES=0.33), and STA (0.17 [0.12:0.23], ES=0.30). These improvements remained (despite minor reductions) for all 4 constructs at 12 months follow-up; HAD (0.25 [0.12:0.39]),

ES=0.40), PAEL (0.06 [-0.05:0.16], ES=0.11), SMI (0.09 [0.00:0.19], ES=0.19), and STA (0.14 [0.04:0.25], ES=0.24). In contrast, no noticeable changes were observed for ED, CAA, SIS, or HSN.

DISCUSSION: Four weeks of personalized MDR effectively improved certain self-management skills (health-directed activities (HDA), positive and active engagement in life (PAEL), self-monitoring and insight (SMI), skill and technique acquisition (STA)) in pwMS. These improvements are likely linked to improvements in health-related quality of life in pwMS.

Interferon-beta exposure in-utero and the risk of infections in early childhood

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HYPOTHESIS: Does in utero exposure to interferon-beta (IFN- β) increased the risk of infection in the first five years of the child?

METHODS: This retrospective matched cohort study utilized data from the Danish Multiple Sclerosis Registry linked with national Danish registries to identify all children born of mothers with MS in Denmark from 1998 to 2018. The study included 510 children exposed to interferon-beta in utero. The children were matched 1:1 on various of demographic characteristics with children born to mothers with untreated MS and 1:3 with children born to mothers without MS. Each child was followed for up to five years. Using individual-level data, we investigated all-cause mortality, rate of hospital admissions due to infections, and redeemed prescriptions of antibiotics. The primary statistical model applied was a negative binomial regression analysis.

RESULTS: We found no differences in childhood mortality, for hospital admissions the rate ratio compared to healthy controls was 0.79 (0.62–1.00). Regarding antibiotic prescriptions, the results were similar (RR 1.00 (0.90–1.11)). Furthermore, we found no certain dose-response relationship between IFN- β exposure duration and hospital admission rate ($P=0.47$) or redeemed antibiotic prescription ($P=0.71$).

DISCUSSION: To our knowledge, this is the first study to investigate the long-term risks associated with in utero IFN- β exposure. In line with other studies on the safety of IFN- β during pregnancy, the results add to the knowledge regarding safety in a reassuring manner.

