PROGRAM

# Nationalt MS Forskningsmøde 2022

30. maj 2022 kl. 9.30-16.30
Scandic Hotel, Vester Søgade 6, 1601 KBH.

DAREMUS
DANSK SELSKAB FOR FORSKNING
I MULTIPEL SKLEROSE

Program for DAREMUS nationalt forskningsmøde 2022 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 Novartis, Roche, Merck, Sanofi Genzyme og Biogen.

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**09.30-10.00** ● **REGISTRERING OG KAFFE**

**10.00-10.10** **Velkommen ved Jeppe Romme Christensen** (formand for DAREMUS).
Lokale: Amalienborg/Fredensborg

**10.10-11.00** DAREMUS-LECTURE:
**Kerstin Hellwig:** Family planning and MS. An update.
Lokale: Amalienborg
Chair: Melinda Magyari

**11.00-12.00** SESSION 1:
**Nominerede projekter til DAREMUS-prisen for MS forskere under 40 år.**
Chair: Tobias Sejbæk
Lokale: Amalienborg

**11.00-11.12** **Betül Okutan:** Progressive multipel sklerose: Trans-cortikal perivaskulær inflammation korrelerer med kliniske mål og nye patologiske mål for cortical plaque-ekspansion.

**11.12-11.24** **Frederik Novak:** Det humorale og cellulære immunrespons fra første til tredje SARS-CoV-2 vaccination konkomitant til anti-CD20 terapi ved multipel sklerose.

**11.24-11.36** **Maria Højberg Knudsen:** Aldersrelateret fald i cerebralt iltforbrug ved attakvis multipel sclerose.

**11.36-11.48** **Rikke Holm Hansen:** Increased Intrathecal Activity of Follicular Helper T Cells in Patients with Relapsing-Remitting Multiple Sclerosis.

**11.48-12.00** **Rolf Holm:** Hvornår starter sekundær progressiv multipel sklerose.

**12.00-12.45** ● **FROKOST**

**12.45-13.00** **Uddeling af DAREMUS-prisen for årets bedste danske videnskabelige projekt.**
Lokale: Amalienborg

**13.00-14.18** PARALLELSESSION 1:
**Immunologisk og symptomatisk behandling af MS.**
Chair: Jette Frederiksen
Chairs: Tobias Sejbæk
Lokale: Amalienborg

**13.00-13.30** KEYNOTE TALK:
**Morten Blinkenberg:** Hæmatopoietisk stamcelle transplantation.

**13.30-13.42** **Elisabeth Framke:** Rebound of clinical disease activity after fingolimod discontinuation? A nationwide cohort study of 992 patients with RRMS in DK.

**13.42-13.54** **Sahla El Mahdaoui:** Intravenøs ofatumumab behandling af multipel sklerose og relaterede sygdomme.

**13.54-14.06** **Sara Mandatori:** IFNβ drives FoxA1+ Tregs cell generation through AMPK-mediated metabolic rewiring.

**14.06-14.18** **Freja Jespersen:** Autologous haematopoietic stem cell transplantation of patients with aggressive relapsing-remitting multiple sclerosis: A Danish single-centre experience.

**13.00-14.18** PARALLELSESSION 2:
**Eksperimentel/paraklinisk skleroseforskning.**
Chair: Finn Sellebjerg
Chairs: Trevor Owens
Lokale: Fredensborg

**13.00-13.30** KEYNOTE TALK:
**Nasrin Asgari:** Diagnostic biomarkers in inflammatory demyelinating disease of the central nervous system: Old and New Ways to Get it Right.

**13.30-13.42** **Anouk Benmamar:** Føtale placentamakrofagers bidrag til graviditetsrelateret forbedring af EAE.

**13.42-13.54** **Sara Samadzadeh:** Microfibril-associated protein 4 (MFAP4) as a biomarker for disease activity of optic neuritis associated-inflammatory demyelinating diseases.

**13.54-14.06** **Bhavya Ojha:** Modeling PMS-like cortical pathology in mouse.

**14.06-14.18** **Shohreh Issazadeh-Navikas:** ADAM12 is a costimulatory molecule that determines Th1 cell fate and mediates tissue inflammation.

**14.20-14.50** **KAFFE**

**14.50-16.32** PARALLELSESSION 3:
**Klinisk og epidemiologisk skleroseforskning**
Chairs: Melinda Magyari
Chairs: Ulrik Dalgas
Lokale: Amalienborg

**14.50-15.20** KEYNOTE TALK:
**Lars Hvid:** The impact of age on disability and key symptoms in MS.

**15.20-15.32** **Finn Boesen:** Casting light into the black box of multi-disciplinary rehabilitation of people with multiple sclerosis- the danish MS hospitals rehabilitation study.

**15.32-15.44** **Josephine Lyng Steenberg:** Udforskning af rammer for integrering af Patient-Rapporterede Oplysninger (PRO) i Det Danske Scleroseregister.

**15.44-15.56** **Magnus Boesen:** Magnetic resonance imaging criteria at onset to differentiate pediatric multiple sclerosis from acute disseminated encephalomyelitis: a nationwide cohort study.

**15.56-16.08** **Malthe Wandall-Holm:** Aldring og arbejdsmarkedstilknytning: Konsekvenserne af et liv med Multipel Sclerose.

**16.08-16.20** **Morten Riemenschneider:** Multimethodological validation of the Modified Fatigue Impact Scale in a Danish population of people with Multiple Sclerosis.

**16.20-16.32** **Mette Dahl Deichmann:** Degeneration of the peripheral nervous system in multiple sclerosis – implications for lower extremity neuromuscular function and physical function.

**14.50-16.32** PARALLELSESSION 4:
**Immunologi og sygdomsmekanismer**
Chairs: Stephan Bramow
Chairs: Zsolt Illes
Lokale: Fredensborg

**14.50-15.20** KEYNOTE TALK:
**Marina Rode von Essen**: CD20 positive T celler ved multipel sklerose.

**15.20-15.32** **Mads Alexander Just Madsen:** Are regional metabolic changes in the primary sensorimotor hand area to structural and functional motor impairment?
- a 7T MR spectroscopy study in multiple sclerosis.

**15.32-15.44** **Marie Mathilde Hansen:** Increased monocyte activity in patients with primary progressive multiple sclerosis.

**15.44-15.56** **Marthe Danielsen:** Sammenhæng mellem abdominal fedme, adipokiner og sygdommens sværhedsgrad hos patienter med multipel sklerose.

**15.56-16.08** **Mathias Falck Schmidt:** Fund af hyperreflektive foci i nethinden ved relapsing remitting multipel sklerose.

**16.08-16.20** **Moschoula Passali:** The association between dietary quality, gut bacterial diversity, and disease severity in patients with multiple sclerosis.

**16.20-16.32** **Liu Yawei:** Suppressive FoxA1+Treg cells prevent tissue inflammation.

**16.32-16.44** **Sepehr Mamoei:** Central and peripheral nervous system changes as markers of disease progression in multiple sclerosis in responders and non-responders to fampridine treatment.

**16.44** **TAK FOR DENNE GANG**

# Abstracts

# Progressive multipel sklerose: Trans-cortikal perivaskulær inflammation korrelerer med kliniske mål og nye patologiske mål for cortical plaque-ekspansion.

**FORFATTERE:** *Okutan, Betül[1]; Houen, Gunnar[1,2]; Sellebjerg, Finn T.[1]; Frederiksen, Jette[1]; Kristensen, Cecilie K.[1]; Jakobsen, Christina[3]; Magyari, Melinda[1,4]; Paunovic, Manuela[6];* Sørensen, *Per Soelberg[1], Scheie, David[5]; Lassmann, Hans[7]; Bramow, Stephan[1,5]*

**INSTITUTION:** [1]Danish Multipel Sklerose Center, Afd. for Hjerne – og Nervesygdomme, Rigshospitalet Glostrup, Danmark, [2]Institut for Biokemi og Molekylær Biologi, Syddansk Universitet, Odense, Danmark, [3]Retsmedicinsk Institut, Københavns Universitet, København, Danmark, [4]Det Danske Scleroseregister, Afd. for Hjerne – og Nervesygdomme, Rigshospitalet Glostrup, Danmark, [5]Afdeling for Patologi, Diagnostisk Center Rigshospitalet, København, Danmark, [6]Department of Neurology, Erasmus University Medical Center, Rotterdam, Netherlands, [7]Brain Research Centre, University of Vienna, Vienna, Austria

**HYPOTESE:** Cortikale plaques er et "hallmark" ved primær (PPMS) og sekundær (SPMS) progressiv multipel sklerose. I en eksporativ post-mortem tværsnitsundersøgelse belyser vi nye patologiske mål for cortikal plaque-ekspansionen i sammenhæng med perivaskulær inflammation i og omkring cortex.

**METODER:** Post-mortem hjernesnit blev mikroskoperet hos 14 PPMS, 12 SPMS samt 22 kontroller farvet for hematoxylin-eosin (HE) og luxol-fast blue (LFB). Unbiased hemisfæresnit og små blokke blev graderet mht. cortikal ekspansiv plaque-aktivitet samt intracortikale, meningeale og juxta-cortikale inflammatoriske perivaskulære mononukleære/lymfocytære infiltrater (PMIs). Journaler og epikriser blev vurderet (blindet for den patologiske analyse). Den gennemsnitlige PMI-størrelse (6-trins semi-kvantitativ skala) og - densitet (#/cm2 hjernevæv, #/cm meninges) blev opgjort i HE farvede snit (én værdi pr. kompartment pr. patient og kontrol). Adaptiv immunaktivering med T og B celler i PMI's blev bekræftet med hhv. CD3 og CD20 i 10/10 patienter (5 PPMS, 5 SPMS, 2 hemisfærecases). Cortikal plaque-ekspansion blev karakteriseret i nabosnit farvet for proteolipid protein (myelin) og CD68 (makrofag/mikroglia). "Aktive" cortikale plaque-områder var makrofag-fyldte med meget vacuoliseret myelin mens "slowly expanding" (SE) områder var smalle plaque-rande med aktiveret mikroglia og diskret vacuolisering. Total "aktive/SE" plaque loads blev opgjort i % af total cortexareal. IgG-deposition i cortikale plaque blev undersøgt ved immunofluorescens i to patienter (en PPMS og en SPMS) vs. en epilepsipatient og en patient med cerebralt B-cellelymfom.

**RESULTATER:** PMI-størrelser korrelerede tæt indbyrdes mellem juxtacorticale intracorticale og meningeale kompartments og med "aktiv/SE" plaque load i cortex. Total plaque load korrelerede derimod kun og moderat med meningeal PMI-denistet. I den poolede stikprøve korrelerede PMI-størrelser (alle kompartments) negativt med alder/overlevelse og progressionsvarighed. "Aktiv/SE" load korrelerede negativt med progressionsvarighed, mens total plaque load korrelerede positivt med seneste EDSS. Der var flere og tættere klinisk-patologiske korrelationer i PPMS end i SPMS. Vi fandt IgG-deposition i cortikale "slowly expanding" plaque-rande.

**DISKUSSION:** Trans-cortical opblussende perivaskulær inflammation (afspejlet ved store PMI's) kan have betydning for cortical plaque-expansion og progressive sygdomsforløb, især ved PPMS. Ophobet inflammation (afspejlet ved høj PMI-denistet) relaterer derimod til total ophobet plaqueload, som igen relaterer til EDSS. Et antistofmedieret immunrespons kan være involveret, men kan også være et uspecifikt fænomen relateret til en beskadiget blod-barriere.

# Det humorale og cellulære immunrespons fra første til tredje SARS-CoV-2 vaccination konkomitant til anti-CD20 terapi ved multipel sklerose

**FORFATTERE:** *Novak, Frederik[1,2]; Bajwa, Hamza Mahmood[1,2]; Nilsson, Anna Christine[3,4]; Nielsen, Christian[3]; Holm, Dorte K.[3]; Østergaard, Kamilla[5]; Bystrup, Anna[6]; Witt, Agnes Hauschultz[6]; Byg, Keld-Erik[4]; Johansen, Isik S.[4,8]; Mittl, Kristen[9]; Rowles, William[9]; Zamvil, Scott S.[9]; Bove, Riley[9]; Sabatino Jr, Joseph J.[9]; Sejbaek, Tobias[1,2]*

**INSTITUTION:** [1]Neurologisk afdeling, Sydvestjysk Sygehus, Syddansk Universitet, Esbjerg, Danmark, [2]Institut for Regional Sundhedsforskning, Syddansk Universitet, Odense, Danmark, [3] Klinisk Immunologisk afdeling, Odense Universitetshospital, Odense, Danmark, [4] Klinisk institut, Syddansk Universitet, Odense, Danmark, [5]Neurologisk afdeling, Nordsjællands Hospital, Hillerød, Danmark, [6]Neurologisk afdeling, Hospitalsenhed Midt, Viborg, Danmark, [7]Reumatologisk afdeling, Odense Universitetshospital, Odense, Danmark, [8]Infektionsmedicinsk afdeling, Odense Universitetshospital, Odense, Danmark, [9]Weill Institut for Neurosciences, Neurologisk afdeling, University California San Francisco, San Francisco, USA

**HYPOTESE:** Det humorale immunrespons er hæmmet ved behandling med anti-CD20 terapi. Antistofdannelsen er reduceret efter bl.a. influenza, pneumokok og tetanus vaccination hos patienter med multiple sklerose (MS) i behandling med ocrelizumab. Studiets hypotese er at det humorale og cellulære respons efter mRNA SARS-CoV-2 vaccination er reduceret. Studiet undersøger niveauerne af specifikke SARS-CoV-2 receptor binding domain (RBD) antistoffer og T-celle reaktivitet. Niveauerne analyseres efter første, anden og tredje mRNA SARS-CoV-2 vaccine hos deltagere med MS i behandling med ocrelizumab.

**METODER:** Et prospektivt, multicenter, longitudinelt studiedesign efter mRNA SARS-CoV-2 vaccination i danske og amerikanske skleroseklinikker. RBD-antistofniveauer blev kvantificeret før og efter administration af vaccine med SARS-CoV-2 IgG II Quant assay (Abbott Laboratories). Oprensningen af B- og T-lymfocytter blev udført ved BD Multitest™6-color TBNK-reagent. Vi målte Spike-specifikt T-celle-responset ved peripheral blood mononuclear cells stimulering med spike peptide pools (JPT Peptide Technologies).

**RESULTATER:** Ud af alle deltagere (n=60) havde henholdsvis 14.0%, 37.7%, 25.0% og 33.3% specifikke RBD-antistoffer efter første og anden vaccination, samt før og efter tredje vaccination. Medianen af antistofkoncentration var henholdsvis 19.8 BAU/ml (range: 9.2 til 254), 74.2 BAU/mL (range: 8.5-2427), 43.7 BAU/mL (range: 7.8-366.1) og 31.3 BAU/ml (range: 7.9-507) efter første og anden vaccination, samt før og efter tredje vaccination. Antistofniveauerne efter anden og tredje vaccination var sammenlignelige (p=0.1475). Andelen af patienter med målbare RBD specifikke antistoffer blev reduceret med 33.3% (p=0.0020) fra anden til tredje vaccination. Vi fandt henholdsvis 0.65 ± 0.08% og 0.95 ± 0.20% spike reaktive $CD4^+$ og $CD8^+$ T-celler efter anden og tredje vaccination.

**DISKUSSION:** Vores resultater viser, at det humorale immunrespons hos patienter i behandling med ocrelizumab er signifikant hæmmet sammenlignet med raske kontroller fra tidligere studier. Samtidig ses et T-celle-medieret immunrespons, som svarer til immunresponset hos raske individer. Det humorale immunrespons målt ved RBD-antistoffer var sammenligneligt efter anden og tredje vaccination. Proportionen af patienter med målbare antistoffer var uændret efter anden og tredje vaccination. Alternativer til mRNA vacciner bør overvejes for at bedre den kliniske beskyttelse imod SARS-CoV-2. Cellulært samt humoralt immunrespons hos patienter der har haft PCR verificeret SARS-CoV-2 efter tredje vaccination vil blive præsenteret på konferencen.

# Aldersrelateret fald i cerebralt iltforbrug ved attakvis multipel sclerose

**FORFATTERE:** *Knudsen, Maria Højberg[1,2]; Cramer, Stig Præsetkjær[1]; Vestergaard, Mark Bitsch[1]; Lindberg, Ulrich[1]; Simonsen, Helle Juhl[1]; Frederiksen, Jette Lautrup[2,3]; Larsson, Henrik Bo Wiberg[1,2]*

**INSTITUTION:** [1]Enhed for funktionel billeddiagnostik, Afdeling for klinisk fysiologi og nuklearmedicin, Rigshospitalet Glostrup, Danmark, [2]Institut for klinisk medicin, Det sundhedsvidenskabelige fakultet, Københavns universitet, København, Danmark, [3]Klinik for synsnervebetændelse og Dansk multipel sklerose center, Afdeling for hjerne- og nervesygdomme, Rigshospitalet Glostrup, Danmark

**HYPOTESE:** Trods sygdomsmodificerende behandling, ses der sygdomsprogression og accelereret cerebral atrofi ved patienter med attakvis multipel sclerose (RRMS). Inflammation påvirker hjernens energiforbrug, og hypotesen er, at den dysregulerede energimetabolisme er en medvirkende faktor til både sygdomsprogression og cerebral atrofi i patienter med multipel sclerose.

**METODER:** Patienter med attakvis multipel sclerose (N = 44) og raske kontroller (N = 36) fik på en 3 Tesla MR-skanner målt globalt cerebralt iltforbrug ved en magnetisk susceptibilitetsvægtet sekvens, blodgennemstrømning ved en fasekontrast sekvens og hjernestørrelse via en højopløsnings 3D T1-vægtet sekvens. Hjerneparenkymfraktionen blev bestemt ved segmentering i FreeSurfer. EDSS blev indhentet fra journaloplysninger fra samme år som skanningen. Statistiske beregninger blev foretaget i R som Welch t-tests og generelle lineære modeller med interaktion mellem kovariaterne alder og sygdomsstatus.

**RESULTATER:** Hjernens iltforbrug var lavere i patienterne sammenlignet med raske kontroldeltagere (patienter: 121.2 µmol/100g/min, kontroldeltagere: 143.2, forskel: 21.9, 95% CI: 7.8 til 36.1, p = 0.002), og faldt med stigende alder relativt til den raske kontrolgruppe (beta = -1.35, p = 0.036). Det lavere iltforbrug kunne forklares af nedsat iltekstraktion (p=0.007) da blodgennemstrømningen ikke var reduceret hos patienter (p= 0.69). Patienterne havde ikke højere atrofigrad, målt som hjerneparenkymfraktion, end kontroldeltagererne. Det cerebrale iltforbrug var hverken korreleret til EDSS score eller læsionsvolumen.

**DISKUSSION:** Vi finder en nedsat cerebral iltmetabolisme i RRMS-patienter før der forefindes cerebral atrofi, og som er på baggrund af nedsat iltekstraktion. Dette støtter hypotesen om mitokondriel dysfunktion hos patienter med RRMS som potentiel sygdomsmekanisme. Hvorvidt reduceret cerebralt iltforbrug afspejler fremtidig atrofi og dermed er en tidlig biomarkør for dette, kræver yderligere studier for at blive belyst. Viden om den ændrede cerebrale energimetabolisme vil forhåbentligt på sigt kunne danne basis for udvikling af nye behandlingsstrategier.

# Increased Intrathecal Activity of Follicular Helper T Cells in Patients with Relapsing-Remitting Multiple Sclerosis

**AUTHORS:** *Hansen, Rikke Holm; Talbot, Jacob; Chow, Helene Højsgaard; Buhelt, Sophie; Hansen, Malene Bredahl; Schwab, Nicholas; Herich, Sebastian; Sellebjerg, Finn; von Essen, Marina Rode*

**INSTITUTION:** Danish Multiple Sclerosis Center, Department of Neurology, Copenhagen University Hospital - Rigshospitalet, Valdemar Hansens Vej 17, Glostrup, Denmark.

**HYPOTHESIS:** Follicular helper T (Tfh) cells play a critical role in protective immunity helping B cells produce antibodies and are likely implicated in the pathogenesis of various autoimmune diseases. This study investigated a possible role of Tfh cells in the pathogenesis of multiple sclerosis (MS).

**METHODS:** We investigated phenotype, prevalence, and function of Tfh cells in blood and cerebrospinal fluid (CSF) from controls and patients with relapsing-remitting MS (RRMS) and primary progressive MS (PPMS) by flow cytometry. Additionally, we assessed the migratory capacity of Tfh cells in patients with MS in an in vitro blood-brain-barrier coculture assay of primary human astrocytes and brain microvascular endothelial cells. CSF concentrations of CXCL13 were analysed using single molecule array.

**RESULTS:** This study identified two phenotypically and functionally distinct Tfh cell populations: CD25- Tfh cells (Tfh1-like) and CD25int Tfh cells (Tfh17-like). Whereas minor differences in Tfh cell populations were found in blood between patients with MS and controls, we observed an increased frequency of CD25- Tfh cells in CSF of patients with RRMS and PPMS and CD25int Tfh cells in patients with RRMS, compared to controls. The frequency of CSF CD25- Tfh cells as well as the CD25- Tfh/Tfr cell ratio correlated positively with the IgG index in patients with RRMS. Despite an increased prevalence of intrathecal Tfh cells in patients with MS, no difference in the migratory capacity of peripheral Tfh cells was observed between controls and patients with MS. Instead, CSF concentrations of CXCL13 correlated positively with total counts of Tfh and Tfr cell subsets in the CSF.

**DISCUSSION:** Our study indicates substantial changes in intrathecal Tfh dynamics, particularly in patients with RRMS, and suggest that the intrathecal inflammatory environment in patients with RRMS promotes recruitment of peripheral Tfh cells rather than the Tfh cells having an increased capacity to migrate to CNS.

# Hvornår starter sekundær progressiv multipel sklerose

**FORFATTERE:** *Holm, Rolf Pringler; Kopp, Tine Iskov; Pontieri, Luigi; Magyari, Melinda*

**INSTITUTION:** Det Danske Scleroseregister, Dansk Multipel Sclerose Center, Neurocentret, Rigshospitalet.

**HYPOTESE:** Overgangen fra attakvis multipel sklerose (RRMS) til sekundær progressiv MS (SPMS) diagnosticeres bagudrettet og er forbundet med stor usikkerhed, idet der ikke findes en paraklinisk undersøgelse, som kan fastslå tidspunktet for transitionen. Projektet vil fastslå længden af usikkerhedsperioden omkring transitionen samt undersøge bidraget fra en SPMS-diagnostisk algoritme.

**METODER:** Via Det Danske Scleroseregister har vi identificeret alle patienter tilknyttet Rigshospitalet, som har fået tildelt forløbsdiagnosen SPMS af en neurolog i perioden 2010-2021. Hos alle patienter med tilgængelige journaloplysninger blev datoen for første omtale af tegn på progression noteret. Differencen mellem denne dato og datoen for tildelt SPMS blev udregnet og defineret som længden af usikkerhedsperioden. Slutteligt blev SPMS-algoritmen fra MS-Base anvendt på populationen for at finde algoritmens bud på transitionsdaten – tiden fra denne dato til datoen for tildeling af SPMS blev ligeledes udregnet.

**RESULTATER:** Studiepopulationens bestod af 143 personer med en gennemsnitsalder på 53 år (SD: 9,7) på tidspunktet for tildeling af SPMS. Patienterne havde en median EDSS på 6,5 (Q1-Q3: 6-7) på tidspunktet for tildeling af SPMS, og 41 personer (28,7%) havde oplevet attakaktivitet i løbet af to år optil tildelingen af SPMS. Kvinderne udgjorde 87 (60,8%) og mændene 56 (39,2%). Gennemsnitslængden af usikkerhedsperioden defineret fra første omtalte tegn på progression til tildelt SPMS var 2,7 år (SD: 2,63). MS-Base algoritmen fastsætter SPMS 4,6 år (DS: 5,60) tidligere end tildeling af SPMS og dermed 1,9 år før første omtale af tegn på progression i journalen.

**DISKUSSION:** Projektets resultater understreger at overgangen fra RRMS til SPMS er forbundet med stor usikkerhed, og at patienter potentielt går flere år i en behandling, der ikke er godkendt til deres sygdomsstadie. Det er første gang, at længden af denne usikkerhedsperiode er blevet undersøgt i en dansk patientpopulation, og resultaterne er i overensstemmelse med de få studier, der findes fra udlandet – de fandt hhv. 2,9 og 3,3 år. Projektets resultater viser desuden, at diagnostiske algoritmer kan have en plads i diagnosticeringen, men at der er en risiko for overdiagnosticering. Behovet for udvikling af parakliniske undersøgelser, som kan hjælpe lægerne til hurtigere diagnosticeringen af SPMS, er således fortsat til stede.

# Rebound of clinical disease activity after fingolimod discontinuation? A nationwide cohort study of 992 patients with RRMS in Denmark

**AUTHORS:** *Framke, Elisabeth; Pontieri, Luigi; Bramow, Stephan; Sellebjerg, Finn; Magyari, Melinda*

**INSTITUTION:** The Danish Multiple Sclerosis Registry, Danish Multiple Sclerosis Centre, Copenhagen University Hospital, Rigshospitalet Glostrup

**HYPOTHESIS:** The aim of our study was to investigate whether disease rebound occurred after fingolimod discontinuation by analyzing clinical disease activity in a large complete population of patients with RRMS in Denmark who discontinued fingolimod treatment. The aim further was to identify clinical and demographical factors associated with risk of disease reactivation after fingolimod discontinuation.

**METHODS:** The study population consisted of 992 patients with RRMS treated with fingolimod for six months or more. We estimated annualized relapse rates (ARR) in five time periods before, during and after fingolimod treatment by fitting negative binominal regression models. We estimated overall ARRs and ARRs stratified by disease activity prior to fingolimod discontinuation. We used multivariable Cox regression to analyze the association between demographic and clinical variables at fingolimod discontinuation and time to first relapse during six months of follow-up after fingolimod discontinuation.

**RESULTS:** During the 12 months prior to fingolimod initiation, the overall ARR was 0.74 (95%CI=0.69-0.80). From fingolimod initiation until six months before discontinuation, the overall ARR was 0.30 (95%CI=0.26-0.33). During the last six months of fingolimod treatment, the overall ARR was 0.58 (95%CI=0.52-0.66). Overall ARRs were 0.56 (95%CI=0.47-0.66) during the first three months and 0.32 (95%CI=0.25-0.40) during the subsequent three months after fingolimod discontinuation. ARRs were higher among patients who discontinued fingolimod due to disease activity than among patients who discontinued fingolimod due to other reasons in all time periods except during the period from three to six months after fingolimod discontinuation where the two groups had similar ARR levels. During follow-up, we identified 117 relapses among the 992 patients who discontinued fingolimod. Lower age, female sex and disease activity prior to fingolimod discontinuation, but not prior treatment with DMT, were statistically significantly associated with an increased risk of experiencing a relapse.

**DISCUSSION:** We did not find evidence for the occurrence of disease rebound after fingolimod discontinuation. The clinical disease activity level after fingolimod discontinuation did not exceed the level during the 12 months before fingolimod initiation. A higher risk of disease reactivation was seen in those with disease breakthrough before fingolimod cessation, in women and in younger patients with MS.

# Intravenøs ofatumumab behandling af multipel sklerose og relaterede sygdomme

**FORFATTERE:** *El Mahdaoui, Sahla[1]; Romme Christensen, Jeppe[1]; Magyari, Melinda[1,2]; Wandall-Holm, Malthe[1,2]; Sellebjerg, Finn[1,3]*

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**HYPOTESE:** Intravenøst administreret ofatumumab er blevet anvendt off-label til multipel sklerose (MS) og relaterede sygdomme, men data er begrænset til et enkelt forsøg med 38 MS-patienter, der fik én infusionsserie. Formålet med studiet var at undersøge sygdomsaktivitet og bivirkninger i relation til længerevarende intravenøs ofatumumab behandling af MS, neuromyelitis optica spektrum sygdom (NMOSD) og myelin oligodendrocyt glycoprotein antistof-associeret sygdom (MOGAD).

**METODER:** Retrospektivt observationelt studie af patienter med MS, NMOSD og MOGAD behandlet off-label med intravenøs ofatumumab ved Dansk Multipel Sklerose Center. Data blev indhentet fra Det Danske Skleroseregister og via journalgennemgang fra behandlingsstart til 6 måneder efter sidste ofatumumab infusion. Vi undersøgte effekten af ofatumumab på den årlige attakrate via negativ binomial regression, og anvendte overlevelsesanalyser til bestemmelse af risikoen for at have oplevet et attak og forværring af EDSS efter 2 års behandling

**RESULTATER:** Vi identificerede 50 patienter (4 med NMOSD, 4 med MOGAD og 42 med MS). Median alder ved behandlingsstart var 46 år (Q1-Q3: 35-52 år), og median EDSS var 4.0 (Q1-Q3: 3.0-5.5). Den årlige attakrate blev reduceret med 58% (95% CI: 41%-70%, p <0.0001) fra 1.03 (95% CI: 0.80-1.33) ved baseline til 0.43 (95% CI: 0.31-0.60) under ofatumumab behandling (median opfølgningstid = 2.6 år). Efter 2 år var sandsynligheden for at have oplevet et attak 55% (95% CI: 69%-41%) og forværring af EDSS 7% (96% CI: 0%-14%). Ved den første infusion oplevede 86% af patienterne infusionsrelaterede reaktioner (IRR), mens 42% oplevede IRR under den sidste infusion. De novo lav IgM blev påvist hos 10/36 patienter, og de novo lav IgG hos ≤3/35. Seks patienter blev indlagt på grund af en infektion. Der var ingen tilfælde af neutropeni.

**DISKUSSION:** Resultaterne indikerer, at intravenøs ofatumumab behandling af MS og relaterede sygdomme reducerer den årlige attakrate og stabiliserer EDSS forværring med en acceptabel bivirkningsprofil. Reduktionen af attakraten var mindre end i studierne af subkutan ofatumumab, men patientgruppen adskiller sig bl.a. herfra ved heterogeniteten af sygdomme, højere alder og EDSS ved baseline samt off-label indikation, hvilket vanskeliggør sammenholdelse hermed. Frekvensen af infusionsreaktioner var relativ høj sammenlignet med ocrelizumab og rituximab, men på linje med fase II studiet af intravenøs ofatumumab.

# IFNβ drives FoxA1+ Tregs cell generation through AMPK-mediated metabolic rewiring

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**HYPOTHESIS:** We hypothesize that IFNβ may contribute to the regulation of metabolic pathways in T cells, and thereby distinctly drive FoxA1+ Tregs cell generation.

**METHODS:** We characterized FoxA1+ Tregs' mitochondrial respiration by using seahorse analyzer. Next, we performed a transcriptomic profile of regulatory T cells exposed to IFNβ identifying metabolic relevant genes and pathways. By taking the advantage from CD4CRE FoxA1 fl/fl mice, we validated selected identified genes. Further we biologically modulated the expression of an identified gene, PRKAG2 to better understand its role during FoxA1+ Treg cell differentiation and metabolic function.

**RESULTS:** We report that the FoxA1+ Tregs differ in their metabolic activity compared to classical FoxP3+ Tregs. The master transcription factor of FoxA1+ Treg cells, FoxA1 induced by IFNβ, reprograms induced-FoxA1+ Tregs' metabolism by interacting with the g subunit of AMPK, enhancing oxidative phosphorylation, ATP production and modulating mitophagy. AMPK activation reprograms energy metabolism to increase mitochondrial respiration and activity in FoxA1 Tregs, but it further induces mitophagy as a recycling process for maintaining healthy mitochondria.

**DISCUSSION:** FoxA1+ regulatory T (FoxA1+ Tregs) cells are a distinct population of regulatory T cells that has been identified in multiple sclerosis (MS) patients benefiting from IFNβ treatment. FoxA1+ Tregs exert anti-inflammatory properties in central nervous system and they are induced by IFNβ, a naturally occurring cytokine. A previous study in our lab revealed that the lack of IFNβ in neurons show mitochondrial defects with accumulation of defective mitochondria. Additionally, few studies show type-I interferons (IFNs) affect metabolism in immune system, however the role of IFNβ in regulating metabolic fluxes in immune cells remains unexplored. Since IFNβ-dependent-FoxA1+ Tregs have been described having beneficial effects in counteracting MS, here we studied IFNβ-induced pathways controlling mitochondrial FoxA1+ Tregs homeostasis. We envisage the understanding of FoxA1+ Tregs cell metabolism will reveal specific targetable pathways to potentiate the positive effects of IFNβ in MS therapy circumventing its major side-effects.

# Autologous haematopoietic stem cell transplantation of patients with aggressive relapsing-remitting multiple sclerosis: A Danish single-centre experience

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**HYPOTHESIS:** This study aims to describe patient characteristics, safety, and efficacy from the Danish experience with autologous haematopoietic stem cell treatment (AHSCT), with the hypothesis, that (AHSCT) is an effective treatment option for patients with aggressive relapsing-remitting multiple sclerosis (RRMS).

**METHODS:** Nationwide cohort study of RRMS patients treated with AHSCT at the Danish Multiple Sclerosis Center, Rigshospitalet, Denmark. Outcome measures were relapse-free survival (RFS), disability worsening-free survival (WFS), MRI event-free survival (MFS), and no evidence of disease activity (NEDA-3) two years post-AHSCT.

**RESULTS:** A total of 32 patients were treated with AHSCT. Seven patients were treated with a myeloablative conditioning regimen of carmustine, etoposide, cytarabine arabinoside, and melphalan (BEAM) and anti-thymocyte globulin (ATG). Twenty-five patients were treated with a non-myeloablative conditioning regimen of cyclophosphamide (CY) and ATG. Median follow-up time for the whole cohort was 39 months (range 11-109), 56% women, median age 38 years (IQR 8.8), median disease duration 6.5 years (IQR 7.3), median baseline Expanded Disability Status Score (EDSS) was 3.75 (IQR 2). The most common acute adverse events (AEs) after conditioning were alopecia (100%), infections (63%), gastrointestinal disorders (81%), thrombopenia (72%), anaemia (41%), and neutropenic fever (41%). Late AEs predominantly consisted of infections including viral reactivation (50%), fatigue (44%), gastrointestinal disorders (31%), thyroid diseases (25%), and premature ovarian insufficiency (88% women). There was no treatment related mortality and only few severe AEs were reported. In the whole cohort, RFS was 77% (95% CI 64-94%), WFS was 79% (95% CI 66-96%), MFS was 93% (95% CI 85-100%), and NEDA-3 was 69% (95% CI 54-89%) at year two post-AHSCT.

**DISCUSSION:** AHSCT is an effective and relatively safe treatment with few serious AEs and no mortality in Danish RRMS patients. However, randomized clinical trials comparing AHSCT with other high efficacy MS disease modifying therapies are still needed.

# Føtale placentamakrofagers bidrag til graviditetsrelateret forbedring af EAE

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**HYPOTESE:** Føtale placentamakrofager udøver en tolerogen aktivitet, der bidrager til graviditetsrelateret undertrykkelse af eksperimentel autoimmun encephalomyelitis (EAE), en dyremodel for multipel sklerose (MS).

**METODER:** Vi undersøgte fænotypen og placeringen af føtale placentamakrofager under hele graviditeten. For at vurdere deres rolle brugte vi to forskellige tilgange. For det første inducerede vi passiv-EAE i gravide mus ved overførsel af encephalitogene T -celler. Vi brugte flowcytometri og histologiske metoder til at spore disse celler og til at vurdere deres interaktion med føtale, placentale makrofager. For det andet inducerede vi aktivt EAE i mus midt i graviditeten og fjernede selektivt føtale, placentale makrofager ved hjælp af en Cre-rekombinase/difteritoksin receptor-tilgang. Resultatet af fjernelsen blev vurderet ud fra sygdoms onset og progression. Desuden brugte vi encellet RNA-sekventering til at karakterisere de cellulære og transkriptomiske forskelle induceret af EAE i placentale leukocytter, især føtale, placentale makrofager. Til sidst brugte vi in vitro-fertilisering af mus for selektivt at ramme interferon signalvejen i føtale celler.

**RESULTATER:** Vi viser, at encephalitogene T-celler er til stede i den murine placenta efter adoptiv overførsel. Desuden når disse celler den føtale labyrint og kan detekteres i nærheden af føtale makrofager, hvilket tyder på en mulig interaktion. Graviditet hos mus har tidligere vist sig at forsinke begyndelsen af EAE-symptomer, hvilket vores resultater bekræfter. Her finder vi, at fjernelsen af fostermakrofager i moderkagen under graviditeten ophæver denne forsinkelse, hvilket giver en tidligere begyndelse af sygdommen. Vores transkriptomiske analyser fremhæver føtal placenta-heterogenitet. Derudover viser vi, at en bestemt delmængde af føtale placentale makrofager, der udtrykker en majoritet af interferon-relaterede gener, induceres i EAE. Selektiv inaktivering af type-1 interferon-signalering viste dog at graviditetsrelateret bedring af MS ikke direkte afhænger af interferon-signaleringen.

**DISKUSSION:** Symptomer på MS og EAE lindres under graviditet gennem en udefineret mekanisme. Vi foreslår her, at placentale immunceller er de centrale aktører i processen. Vores undersøgelse fokuserer på føtale makrofager i placenta og undersøger deres potentielle rolle i induktionen af et tolerogent miljø, der ligger til grund for en graviditetsrelateret beskyttelse mod MS/EAE. At øge vores forståelse af de mekanismer, der dæmper sygdommen, kan i sidste ende være nyttig til udvikling af nye terapier.

# Microfibril-associated protein 4 (MFAP4) as a biomarker for disease activity of optic neuritis associated-inflammatory demyelinating diseases.

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HYPOTHESIS: Regional differences in blood-brain-barrier (BBB) permeability may explain disease activity in inflammatory demyelinating diseases (IDDs). Microfibrillar-associated protein 4 (MFAP4) is an extracellular matrix protein with binding capacity for collagen IV, an essential component of the BBB. MFAP4 has not been described in CNS. We hypothesize that MFAP4 protein is localized on the CNS microvascular endothelial cells and alteration of MFAP4 expression occurs in IDDs.

METHODS: MFAP4 levels were determined in duplicate by AlphaLISA in cerebrospinal fluid (CSF) and serum from 169 IDDs patients from eight centers (138 acute, 31 non-acute). Glial fibrillary acidic protein (GFAP) and neurofilament light chain (NfL) were measured using Simoa. Samples were analyzed blindly and compared to healthy controls (HC). Tissues from CNS autopsy were investigated from patients with multiple sclerosis (MS) (acute MS; n=3 and progressive MS; n=3), neuromyelitis optica spectrum disorder (NMOSD; n=2), as well as optic nerve from one NMOSD patient, disease controls (patients with stroke (n=3)) and HC (n=4). Paraffin sections were stained using antibodies against MFAP4.

RESULTS: CSF MFAP4 levels were significantly reduced in patients with acute optic neuritis (ON) (mean U/mL: 14.6) compared to HC (17.9; p=0.009) and to other CNS attacks (17.2; p=0.030). CSF MFAP4 levels in acute IDDs were negatively correlated with severity of the relapse (r=-0.42, p=0.015). CSF MFAP4 levels were positively correlated with NfL levels in IDDs (r=0.21, p=0.0431) and with GFAP levels in NMOSD (r=0.34, p=0.037). MFAP4 was expressed in the meninges and around blood vessels; expression was enhanced in normal optic nerve. In the acute stage in NMOSD distant from lesions, MFAP4 expression was increased in meninges. Loss of MFAP4 immunoreactivity co-localized with aquaporin-4 loss in NMOSD lesions.

DISCUSSION: MFAP4 may serve as a marker of disease activity in both ON and other CNS attacks. MFAP4 as an extracellular matrix protein is expressed in CNS vessels, optic nerve, and meninges. Absence of MFAP4 in the well-established NMOSD lesion may relate to the fact that the astrocytes are the target as well as the source of MFAP4. Our data suggest that MFAP4 is a marker of matrix remodeling processes during BBB disruption in IDDs.

# 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 0.2% cuprizone for 6 weeks. We delivered cytokines in subarachnoid space, followed by intrathecal injection of LPS or microglia primed in 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 beam to induce a focal burn injury in the cortex.

**RESULTS:** We induced cortical inflammation by feeding the myelin toxin cuprizone to mice. Preliminary data showed small aggregates of activated microglia in cortical grey matter. These aggregates were intensified by subarachnoid injection of cytokines and by intrathecal injections of lipopolysaccharide or neurodegeneration-primed microglia. Similar focal subpial microglial activation was induced by non-invasive laser irradiation.

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

# ADAM12 is a costimulatory molecule that determines Th1 cell fate and mediates tissue inflammation

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**HYPOTHESIS:** A disintegrin and metalloproteinase (ADAM)12 was previously found to be expressed in T cells in the inflamed brain. We assumed that ADAM12 is functional on T-cell responses in general and in tissue inflammation which has not been examined.

**METHODS:** Here, we studied the role of ADAM12 in T-cell responses, fate determination on activation, and its functions in T cells to mediate tissue inflammation. This was achieved by utilizing ADAM12 knockout (KO) mice and immunize for experimental autoimmune encephalomyelitis, the model for MS and compared to their wildtype (WT) littermates, exerted RNA-sequencing of T cells from ADAM12KO and WT and study their functions in vitro and in vivo.

**RESULTS:** We identified ADAM12 as a costimulatory molecule that is expressed on naive T cells and downregulated on stimulation. ADAM12 mimics CD28 costimulatory signaling to activate and induce the proliferation of T-helper 1 (Th1) cells. Monoclonal ADAM12 Fab antibodies trigger T-cell activation by amplifying TCR signaling to stimulate T-bet-mediated IFNγ production. Lack of genomic ADAM12 and its knockdown in T cells diminished T-bet and IFNγ production in Th1 cells, whereas other T cells, including Th17 cells, were unaffected. ADAM12 had similar functions in vivo on myelin antigen (MOG35-55)-induced T-cell activation. We found that genetic loss of ADAM12 profoundly alleviated Th1-mediated neuroinflammation and thus disease severity in experimental autoimmune encephalomyelitis, a model of multiple sclerosis. Transcriptomic profiling of MOG35-55-specific ADAM12-/- T cells revealed differentially expressed genes that are important for T-cell activation, proliferation, and costimulatory signaling and Th1 pathogenicity, consistent with their inability to cause T-cell-mediated skin inflammation in a model of adoptive delayed-type hypersensitivity.

**DISCUSSION:** We conclude that ADAM12 is a T-cell costimulatory molecule that contributes to the pathogenesis of tissue inflammation and a potential target for the treatment of Th1-mediated diseases like MS.

# Casting light into the black box of multi-disciplinary rehabilitation of people with multiple sclerosis- the danish MS hospitals rehabilitation study

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**HYPOTHESIS:** Rehabilitation is an important and integral part of the Danish national Multiple Sclerosis (MS) health management strategy. Boesen et al. (2020) showed a significant long-term effectiveness of inpatient multidisciplinary rehabilitation (MDR) on functioning and health-related quality of life (HRQoL). However, little is known about the interplay of MS patients' heterogenous challenges, received MDR services, and its impact on rehabilitation effectiveness, a phenomenon referred to as the 'black box of rehabilitation'. Here, we investigated this interplay hypothesis by investigating MDR treatment effects on HRQoL as a function of patient's main challenges, conceptualized as five main focus areas (MFAs): Resilience, Cognitive Function, Energy, Physical Function and Personal Needs.

**METHODS:** Prior to MDR patients were MFA-assigned after a goal-setting consultation with a case manager and certified coach. We used the Functional Assessment in Multiple Sclerosis (FAMS) and its six subscales, covering diverse aspects of HRQoL, as outcome variables at baseline, discharge and 12-months follow-up (MFU). Study design and methods followed Boesen et al. (2020) with slight modifications, e.g., including a treatment × MFA interaction effect.

**RESULTS:** MFAs showed significant differences in terms of demographic, clinical and HRQoL characteristics at baseline indicating that MFAs differentiate with HRQoL and disease progression state. All MFAs showed significant improvement at discharge (FAMS, $p < 0.05$). Estimated FAMS 12 MFU controlled treatment effects were found to be +12.7 (Resilience, $p = 0.001$, $n = 62$), +9.5 (Cognitive function, $p = 0.056$, $n=55$), +11.3 (Energy, $p = 0.004$, $n = 125$), +0.3 (Physical function, $p = 0.94$, $n = 137$), +17.8 (Personal needs, $p = 0.036$, $n = 11$) against +4.7 FAMS units found in the whole study population, $p <0.001$, $n = 413$).

**DISCUSSION:** Our study demonstrated that individualized MDR improves HRQoL in MS patients dependent on a patient's MFA, with the degree and duration of the benefits, as well as the affected sub-dimensions of HRQoL being associated with rehabilitation goals and received services. We found some evidence that MFA changes with disease progression state pointing towards the importance of regular patient reviews and differentiated MDR to achieve maintained functional capacity and performance in people with MS.

# Udforskning af rammer for integrering af Patient-Rapporterede Oplysninger (PRO) i Det Danske Scleroseregister

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**HYPOTESE:** For at styrke inddragelsen af personer med Multipel Sclerose (PmMS), og højne kvaliteten i deres behandling, ønsker Det Danske Scleroseregister at anvende Patient-Rapporterede-Oplysninger (PRO) i mødet mellem patient og sundhedsprofessionel. Formålet med dette projekt er at undersøge, hvordan brugen af PRO-data kan blive meningsfuld for både PmMS og fagpersoner.

**METODER:** Projektet består af tre faser: 1) Gennem et systematisk litteraturstudie kortlægges de seneste 10 års internationalt publicerede spørgeskemaer til indrapportering af PRO på MS-området, samt omfanget af patientinddragelse i forbindelse med udvikling af disse PRO-værktøjer. 2) Gennem fokusgruppeinterviews og individuelle interviews undersøges PmMS' præferencer ifm. rapportering af PRO. Datamaterialet analyseres med afsæt i en tematisk analyse. 3) Gennem en workshop undersøges MS-sundhedsprofessionelles perspektiver på PRO, og hvordan brugen af PRO bliver meningsfuld for dem.

**RESULTATER:** Resultater fra litteraturstudiet indikerer et behov for øget inddragelse af PmMS i udviklingen af PRO-værktøjer, hvis anvendelsen skal være relevant for patientgruppen. Resultater fra interviewundersøgelsen og workshoppen viser, at PRO bør anvendes aktivt og som et dialogværktøj i mødet mellem patient og sundhedsprofessionel. PRO må ikke være tidskrævende for PmMS at udfylde eller for den sundhedsprofessionelle at anvende. PRO bør omfatte neurologiske symptomer, kognitive funktionsnedsættelser, mental sundhed, egenomsorg og sociale udfordringer relateret til MS. Dog bør dette afstemmes ift. den sundhedsprofessionelles kompetencer for at den sundhedsprofessionelle oplever at kunne give evidente råd om symptomer og behandling, og for at patienten modtager den bedst mulige behandling. Da symptomprofilen for PmMS kan variere, bør PRO-spørgeskemaer kunne tilpasses den enkelte patient.

**DISKUSSION:** PmMS og MS-sundhedsprofessionelle ser et potentiale i at anvende PRO i MS-behandlingen. Anvendelsen af PRO vil kræve ekstra tidsforbrug i en klinisk praksis, der i forvejen er tidspresset for MS-sundhedsprofessionelle. Desuden kan udfyldelsen af PRO for nogle PmMS opleves som en registreringsbyrde. Gevinsten ved at anvende PRO bør derfor være tydelig for begge parter. Anvendelsen af PRO kan have flere forskellige formål, herunder både til patientinddragelse, sygdomsmonitorering og forskning. I dette projekt er det relevant at fastholde, at PRO først og fremmest skal styrke dialogen mellem patient og sundhedsprofessionel. Næste fase af undersøgelsen vil fokusere på implementeringen af de foreløbige resultater i de nationale MS-klinikker.

# Magnetic resonance imaging criteria at onset to differentiate pediatric multiple sclerosis from acute disseminated encephalomyelitis: A nationwide cohort study

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**HYPOTHESIS:** Brain MRI is the critical in distinguishing pediatric MS from acute disseminated encephalomyelitis (ADEM). Our aim was to propose MRI criteria to distinguish MS from monophasic ADEM based on the first brain MRI and to validate previously proposed MRI criteria.

**METHODS:** A neuroradiologist undertook retrospective evaluation of the MRI at the first demyelinating event in children (<18 years) with medical record-validated MS and ADEM in Denmark during 2008–15. We used forward stepwise logistic regression to identify MRI categories that differed significantly between MS and ADEM. We estimated accuracy statistics for all MRI criteria to distinguish MS from ADEM.

**RESULTS:** The monophasic ADEM cohort (n=46) was nationwide and population-based during 2008–15; the median age at onset of 5.3 years (range 0.8–17.2) and children had at least five years of follow-up to ensure a monophasic disease course. Children with MS (n=67) had a median age at onset of 16.3 years (range 3.3–17.9). Having at least two categories best distinguished MS from monophasic ADEM by an area under the curve of 83% to 89%: (a) corpus callosum long axis perpendicular lesion; (b) only well-defined lesions; (c) absence of basal ganglia or thalamus lesion OR (a) corpus callosum long axis perpendicular lesion; (b) only well-defined lesions; (c) absence of diffuse large lesions; (d) black holes. The Callen, KIDMUS, and IPMSSG criteria performed well. The McDonald 2017, Barkhof, MAGNIMS, and Verhey criteria had poorer performance.

**DISCUSSION:** This study provides Class II evidence that brain MRI has good performance in differentiating MS from monophasic ADEM at onset.

## Aldring og arbejdsmarkedstilknytning: Konsekvenserne af et liv med Multipel Sclerose

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**HYPOTESE:** Den gradvist tiltagende funktionsnedsættelse af patienter med multipel sclerose (MS) påvirker arbejdsevnen negativt. Der er kun forsket sparsomt i samspillet mellem aldring og arbejdsevnetab. Formålet med studiet er at kvantificere tabet af arbejdsevne gennem et liv med MS målt på forskellige socioøkonomiske endemål.

**METODER:** Landsdækkende observationelt kohorte-studie baseret på data fra Det Danske Scleroseregister koblet på individ-niveau til nationale befolkningsregistre. Alle patienter med MS samt personer fra et tilfældigt udsnit på 25% af den danske befolkning var kandidater til inklusion i kohorten. Studieperioden forløb fra den 1. januar 1992 til den 1. januar 2019. Inklusionskriterierne var en alder mellem 18 og 65 i studieperioden, at være i live på et tidspunkt i studieperioden samt ikke at have modtaget førtidspension forud for inklusion. Studiet havde to endepunkter: To år uden indkomst forudgået af mindst ét år med indkomst og tildeling af førtidspension. Patienterne blev fulgt separat for hvert endepunkt til forekomsten af et endepunkt, død, emigration, 65-års fødselsdag eller administrativ censurering d. 1. januar 2019. Vi estimerede hazard-ratioer ved hjælp af årssagsspecifikke Cox-regressions-modeller, hvor individer bidrog med risiko-tid i aldersgrupper (18-24,25-34,35-44,45-54,55-64) og i en binær eksponeringsvariabel (MS/ikke-MS). Vi beregnede absolutte risici justeret for konkurrerende årsager ved hjælp af Aalen-Johansen estimatoren.

**RESULTATER:** Den endelige kohorte bestod af 1.321.784 personer, hvoraf 16.030 patienter havde eller udviklede MS i studie-perioden og 1.305.754 var kontroller fra befolknings-udsnittet. Sammenlignet med baggrundsbefolkningen var der en betydeligt større risiko for tab af lønindkomst i MS-gruppen over alle aldersgrupper med et maksimum i aldersgruppen 45-54 (HR: 4.0; 95% CI: 3.8-4.2) og tilsvarende større risiko for tildeling af førtidspension i MS-gruppen over alle aldersgrupper med et maksimum i aldersgruppen 25-34 (HR: 22.6; 95% CI: 20.9-24.4). Den absolutte risiko for en 40-årig person med MS for at have oplevet tab af lønindkomst var 60.2% (95% CI: 57.7-62.8) og for tildeling af førtidspension 56% (95% CI: 53.8-58.6).

**DISKUSSION:** Danske patienter med MS har en høj risiko for indkomsttab og tildeling af førtidspension sammenlignet med baggrundsbefolkningen i hele den arbejdsdueligе alder. Studiet illustrerer den relative socioøkonomiske nedgang oplevet af patienter med MS og dermed indirekte den økonomiske byrde for samfundet og individet.

# Multimethodological validation of the Modified Fatigue Impact Scale in a Danish population of people with Multiple Sclerosis

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**HYPOTHESIS:** Fatigue is the most common symptom reported by patients with multiple sclerosis (pwMS), and it is known to have a detrimental impact on patients' perception of health and quality of life. Subjective perceptions of fatigue is often measured by the Modified Fatigue Impact Scale (MFIS) – an acknowledged outcome measure in clinical trials. However, despite being widely used in the Danish MS community, the Danish translation of the questionnaire has not yet been validated. Moreover, previous validation studies of other translations of the MFIS scale have reached different conclusions regarding the validity of the MFIS. Therefore, we provide a multimethodological validation of MFIS in compliance with the COnsensus-based Standards for the selection of health status Measurement INstruments (COSMIN) guidelines using a large Danish population of pwMS.

**METHODS:** Factor analytic and multidimensional Rasch analytic methods were applied to investigate the structural validity of MFIS. Moreover, measurement and bi-factor models were applied to address divergence and convergence. McDonalds ωt was used to assess reliability. Cross-cultural and nomological validity was assessed in relation to relevant external populations and constructs, respectively. Responsiveness was evaluated following one month of multi-disciplinary rehabilitation (MDR).

**RESULTS:** Based on data from 424 Danish MS patients, the MFIS showed an acceptable fit to both factor analytic and multidimensional Rasch models. MFIS was found to be dominated by a general factor but with considerable substructure present. Sufficient divergence was found between cognitive and physical subdomains, but not the psychosocial subscale. Mc Donald's ωt of 0.96 indicated good reliability of the scale, however, with low specific reliability of the psychosocial subscale. Homogeneity across Danish and European populations of pwMS supported cross-cultural validity. Explorative factor analysis of the nomological network of MFIS revealed expected convergence with cognitive and physical aspects. MFIS showed good responsiveness as indicated by moderate to large effect sizes following MDR.

**DISCUSSION:** The Danish version of the MFIS showed good reliability, a good structural, cross-cultural, and nomological validity an acceptable fit to a multidimensional Rasch analysis, and a good responsiveness. The psychosocial subscale of the MFIS however should be interpreted with caution.

# Degeneration of the peripheral nervous system in multiple sclerosis – implications for lower extremity neuromuscular function and physical function

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**HYPOTHESIS:** While multiple sclerosis (MS) is a disease of the central nervous system, the peripheral nervous system (PNS) also undergoes deleterious changes. Periheral nerve stimulation have shown reduced compound muscle action potential (CMAP) amplitude (~function) and number of functional motor units (MUs; ~structure) in persons with MS. We hypothesize that PNS degeneration in the lower extremity is accompanied by reductions in neuromuscular function (e.g. muscle strength) and physical function (e.g. walking capacity).

**METHODS:** A total of n=29 participants were enrolled: MSmild (patient determined disease steps (PDDS) score 0-2; n=14 (9 females), age 44±12 years), MSmoderate (PDDS score 3-7, n=7 (5 females), age 55±8 years), and healthy controls (HC; n=8 (5 females), age 49±11 years). Using the novel MScanFit MUNE technique (a semi-automatic peripheral nerve stimulation protocol), CMAP amplitude and MUs were determined in m. tibialis anterior (TA; involved in dorsiflexion). Using the HUMAC isokinetic dynamometer, dorsiflexion maximal muscle force (DFmvc) and sustained 20% force steadiness (DFfs) were determined. Also, 6-minute walk test (6MWT; involving dorsiflexion) was determined. Data are shown as mean±sd.

**RESULTS:** Disease progression (i.e. HC vs MSmild vs MSmoderate) was accompanied by marked reductions ($p<0.05$) in TA MUs (125±37 vs 95±52 vs 55±51) and CMAP amplitude (7.2±1.7 vs 6.4±1.0 vs 5.7±1.9 mV). A parallel pattern of changes were observed for DFmvc (1.37±0.27 vs 1.25±0.25 vs 0.94±0.27 Nm/kg), DFfs (HC 1.67±1.18 vs 1.96±1.56 vs 3.85±3.92 CV%), and 6MWT (707±73 vs 625±91 vs 400±107 m).

**DISCUSSION:** Our data suggest that degeneration of the PNS (CMAP, MUs) follows disability progression of MS, with greater deleterious changes in MSmoderate > MSmild > HC. This was accompanied by a parallel pattern of changes in lower extremity neuromuscular function (DFmvc, DFfs) and physical function (6MWT). Degeneration of the PNS appear to have detrimental consequences for physical functional capacity in persons with MS.

# Are regional metabolic changes in the primary sensorimotor hand area to structural and functional motor impairment? – a 7T MR spectroscopy study in multiple sclerosis

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**HYPOTHESIS:** Multiple Sclerosis (MS) alters regional brain metabolism, but how do regional metabolic changes relate to local and distant brain function and structure of the involved pathway? In this study we characterized the metabolite profile of the left and right sensorimotor hand area (SM1-HAND) in patients with MS. Our hypothesis was that regional metabolic changes are associated with local and pathway related changes in structural and functional integrity.

**METHODS:** 47 MS patients (34 relapsing remitting (RR), 13 secondary progressive (SP)) and 23 healthy control (HC) participants underwent single-voxel 7T magnetic resonance spectroscopy (MRS) to characterize the metabolic profile of the left and right SM1-HAND. We also acquired structural 7T-MRI to measure local and pathway related brain and lesion volumetrics, along with fractional anisotropy (FA) and mean diffusivity (MD) of the corticospinal tract (CST). Sensorimotor testing included the 9-hole peg test and corticospinal conduction was measured with transcranial magnetic stimulation (TMS).

**RESULTS:** Using mixed linear models corrected for age, gender and tissue fraction of the MRS-voxel, we found that regional N-acetyl-aspartate (NAA) – a marker of neuronal density, glutamate and creatine concentrations were lower in MS patients compared to HCs. This effect seemed to be stronger for SPMS patients. Interestingly, we did not find any differences in myo-inositol – a glial marker, in contrast to previous findings. There was no relationship between the local lesion volume of the MRS voxel and any metabolites. Interestingly we found a correlation between NAA of the SM1-HAND and atrophy of the CST along with CST lesion volume and mean MD values. Glutamate and NAA levels correlated with CST conduction times, but only weakly with performance on the 9-hole peg test.

**DISCUSSION:** The neurochemical profile of the primary sensorimotor hand area is altered in MS, particularly in patients with SPMS. Our results suggest that this change may be driven by distant pathology of the connected pathway rather local changes within in the voxel. There findings may indicate sensitivity of MRS towards retrograde axonal and neuronal degeneration.

# Increased monocyte activity in patients with primary progressive multiple sclerosis

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**HYPOTHESIS:** We hypothesize that the prevalence of monocytes in patients with RRMS and PPMS is different compared to healthy controls, and that the monocytes are more activated due to disease activity.

**METHODS:** Peripheral blood monocytes from healthy controls (n = 35), untreated patients with RRMS (n = 35), untreated patients with PPMS (n = 38), and patients with RRMS treated with ofatumumab (n = 17), dimethyl fumarate (n = 20) or alemtuzumab (n = 15) were analyzed by flow cytometry. Monocytes were defined as $CD14^+$ and further divided into the functionally different $CD16^-$ and $CD16^+$ subtypes. Activated monocytes were defined as $CD40^+$.

**RESULTS:** We found an increased absolute count of $CD14^+CD16^-$ monocytes in blood of patients with PPMS compared to healthy controls and, furthermore, that the activation of both CD14+CD16- and CD14+CD16+ monocytes in patients with PPMS was increased. No difference in monocyte prevalence or activation was observed in patients with RRMS compared to healthy controls. In patients with RRMS treated with one of the three included disease modifying treatments, we found no change in absolute counts or activation status of monocytes.

**DISCUSSION:** Our data provide evidence of increased blood monocyte counts and activation in patients with PPMS but not in treatment naïve patients with RRMS. Also, no change was observed in patients treated with ofatumumab, dimethyl fumarate or alemtuzumab. Consistent with previous findings, our study therefore indicates an involvement of innate immunity in the pathogenesis of progressive MS.

# Sammenhæng mellem abdominal fedme, adipokiner og sygdommens sværhedsgrad hos patienter med multipel sklerose.

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**HYPOTESE:** Multipel sklerose (MS) er karakteriseret ved neurodegeneration i centralnervesystemet (CNS). Fedme i ungdomsårene er blevet identificeret som en risikofaktor for MS, men mekanismerne er stadig uklare. Fedtvæv – især visceralt fedtvæv – er et endokrint organ, der udskiller adipokiner med immunregulerende funktioner, men data om den potentielle effekt af adipokiner på MS-sygdommens sværhedsgrad er stadig sparsomme. Denne undersøgelse har til formål at identificere potentielle forskelle i kropssammensætning og niveauer af adipokinerne leptin, adiponectin og resistin mellem patienter med MS og raske kontroller (HC'er). Derudover vil de potentielle sammenhænge mellem kropssammensætning, cirkulerende niveauer af ovennævnte adipokiner og sygdoms sværhedsgrad blive undersøgt.

**METODER:** I dette tværsnits-case-kontrol-studie blev i alt 80 MS-patienter og 47 HC'er rekrutteret fra Dansk Multipel Sclerose Center (DMSC). Kropssammensætning blev vurderet ved hjælp af body mass index (BMI), talje-til-hofte-forhold (WHR) og sagittal abdominal diameter (SAD). Serumkoncentrationen af adipokinerne leptin, adiponectin og resistin blev målt ved enzymbundet immunosorbent-assay (ELISA). Multiple Sclerosis Severity Score (EDSS) og den årlige tilbagefaldsrate blev beregnet baseret på data fra COMPOS scleroseregisteret. Desuden besvarede MS-patienter den validerede spørgeskematræthedsskala (FSS). Kognitiv funktion, fingerbehændighed og gangevne blev evalueret ved hjælp af henholdsvis symbol digit modalities test (SDMT), 9-hullers-peg-test (9-HPT) og timet 25-fods gangtest (T25FWT).

**RESULTATER:** Adiponectin-niveauer var signifikant højere blandt MS-patienter (gennemsnit=8860 ng/mL, IQR=5802-12430) sammenlignet med HC'er (middel=7334 ng/mL, IQR=4574-8740), og leptin- og adiponectin-niveauer var højere blandt kvinder sammenlignet med mænd inden for samme kohorte. Blandt alle deltagere opstod der korrelationer mellem leptin og BMI (korr=0.750, $p$<0.001) og SAD (korr=0.759, $p$<0.001) og mellem adiponectin og alle kropsparametre (BMI: korr=-0.179, $p$=0.045, WHR: korr=-0.315, $p$<0.001, SAD: korr=-0.218, $p$=0.014). MSSS korrelerede med BMI (korr=0.263, $p$=0.018), WHR (korr=0.231, $p$=0.040), SAD (corr=0.377, $p$<0.001) og leptin (korr=0.291, $p$=0.009). Attak-rate korrelerede med BMI (corr=0.288, $p$=0.010), SAD (corr=0.305, $p$=0.006) og leptin (corr=0.234, $p$=0.038). T25FWT korrelerede med BMI (corr=0.40, $p$=0.035), SAD (corr=0.45, $p$=0.007) og leptin (corr=0.41, $p$=0.027).

**DISKUSSION:** Dette studie understøtter en sammenhæng mellem BMI og visceralt fedt i henhold til adipokiner (leptin, adiponectin og resistin) og sværhedsgraden ved MS. Forskelle i adiponectin-niveauer blev fundet mellem patienter og HC'er, og det blev observeret kønsforskelle i niveauer af leptin og adiponectin.

# Fund af hyperreflektive foci i nethinden ved relapsing remitting multipel sklerose

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**HYPOTESE:** At potentielle patologiske celler i nethinden kan identificeres hos patienter med relapsing remitting multipel sklerose (RRMS)

**METODER:** I dette eksplorative tværsnitsstudie undersøgte vi forekomsten af hyperreflektterende elementer i nethinden hos 44 RRMS-patienter (88 øjne) og fra 40 raske kontroller (80 øjne). Alle patienter gennemgik højopløselig nethindescanninger med optisk kohærenstomografi (SD-OCT). I alt blev 20160 OCT B-scanninger systematisk analyseret i henhold til distinkte morfologiske træk ved hyperreflekterende strukterer i det ydre kernelag af nethinden.

**RESULTATER:** Vi identificerede i ydre kernelag af nethinden hos patienter med RRMS karakteristiske hyperreflekterende foci (HF) og fandt, at RRMS patienter besad en signifikant højere forekomst af HF i det ydre kernelag af nethinden sammenlignet med raske kontroller ($p < 0{,}001$). SD-OCT viste, at 64,1 % af HF var placeret mod midten af nethinden (1400 µm i horisontal afstand fra midten af macula). Ingen korrelation fundet imellem HF og den gennemsnitlige retinale nervefiberlag eller gangliecellelags tykkelse. ($p= 0{,}37$ , $p=0{,}52$)

**DISKUSSION:** Studiet tilvejebringer evidens for et potentielt nyt patologisk fund hos RRMS-patienter da ingen hypperreflektive foci endnu er identificeret hos 40 raske kontroller. Hyperreflektive foci kan repræsentere retinal mikroglia, og yderligere prospektive undersøgelser med større sample size er afgørende for forstå den patogene rolle af hyperreflektive foci i multipel sklerose.

# The association between dietary quality, gut bacterial diversity, and disease severity in patients with multiple sclerosis

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**HYPOTHESIS:** Dietary quality affects multiple sclerosis (MS) disease severity possibly through modulating gut bacterial diversity

**METHODS:** 78 MS patients and 47 healthy household controls (HHCs) were recruited. Dietary intake was assessed by weighted dietary registries of three non-consecutive days. Three dietary guidelines were studied: intake of fruits & vegetables (FV) ≥ 600 g/10 MJ/day, fiber intake ≥ 30g/10 MJ/day, and saturated fatty acid (SFA) intake ≤ 10 E%. Gut bacterial diversity was assessed by 16s rRNA sequencing. α-diversity was evaluated using Shannon-Wiener diversity index and observed features. β-diversity was evaluated using Bray-Curtis and weighted UniFrac distances. Disease severity was assessed using MS Severity Score (MSSS) & SymptoMScreen.

**RESULTS:** Out of 65 MS patients who completed the dietary registries only 57% adhered to at least one of the selected dietary guidelines, and only 5 MS patients (13.5%) adhered to all three. More specifically, 19% had a FV intake ≥ 600 g/10 MJ/day, 32% had a fiber intake ≥ 30g/10 MJ/day, and 39% had a SFA intake ≤ 10 E%. MSSS correlated with SFA intake in g/day (rho=0.267, p=0.0316) and g/MJ/day (rho=0.247, p=0.0478). MS patients and HHCs had similar dietary quality and there were no differences in α-diversity between the two groups. However, we found significant differences in β-diversity between MS patients and HHCs (weighted UniFrac, p=0.021 & Bray-Curtis, p=0.047). When grouped based on disease severity or dietary intake (low vs medium vs high), we found differences in β-diversity between patients with high vs low SymptoMScreen score (Bray-Curtis, p=0.007, q=0.0210) and patients with high vs low intake of FV (weighted UniFrac, p=0.001, q=0.003), but not between patients with high vs low intake of SFA.

**DISCUSSION:** Our data support that most Danish MS patients do not comply with the national dietary guidelines. Intake of SFA positively correlated with MS disease severity, however, intake of SFA did not affect gut bacterial diversity. We found differences in β-diversity, but not in α-diversity when comparing patients with MS to HHCs. Future, studies should aim at clarifying the cause of gut bacterial alterations in MS and evaluate whether reducing intake of SFA can ameliorate MS.

# Suppressive FoxA1+Treg cells prevent tissue inflammation

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**HYPOTHESIS:** Th17 cells are shown to participate in the pathogenesis of many autoimmune and inflammatory diseases, including Multiple Sclerosis (MS). In contrast to Th1 and Th2 cells, which represent relatively stable T cells subsets, Th17 cells display remarkable plasticity. Cytokines, as a part of environmental cues, are essential in contributing to Th17 cell plasticity. As IFNβ can generate FoxA1+ Treg cells, we investigated IFNβ's role in the plasticity of Th17 cells.

**METHODS:** We have examined in vitro differentiated murine Th17 cells and naturally occurring human Th17 cells. Upon IFNβ treatment, we were able to convert Th17 to FoxA1+Treg cells (thereby termed Th17iFoxA1+Treg cells). With naturally occurring human Th17 cells, we applied an unbiased RNA-seq and ChIP-seq to compare Th17 cells vs. naïve T cells and Th17iFoxA1+Treg cells vs. Th17 cells. We identified several signature genes of Th17iFoxA1+Treg cells. In addition, we have also used Th17-induced adoptive transfer models of EAE (experimental autoimmune encephalomyelitis) and DTH (delayed-type hypersensitivity) to illustrate the Th17iFoxA1+Treg cells' suppressive function in vivo.

**RESULTS:** We have demonstrated that IFNβ reprograms Th17 cells to become iFoxA1+Treg cells (Th17iFoxA1+Treg cells). Th17iFoxA1+Treg cells hold unique transcriptomic and epigenomic profiles based on unbiased RNA-seq and ChIP-seq analysis. Th17iFoxA1+Treg cells display a suppressive function by inhibiting T cells' proliferation, as well as limiting Th17-induced inflammation in animal models for MS i.e. EAE, and for skin inflammation; DTH.

**DISCUSSION:** We have identified that FoxA1+Treg cells are reprogrammed from Th17 cells by IFNβ both in humans and mice. From these results, we conclude that Th17-driven Th17iFoxA1+Treg cells are behaving similarly to the FoxA1+Treg cell population, and are playing a critical role in controlling Th17-mediated tissue inflammation.

# Central and peripheral nervous system changes as markers of disease progression in multiple sclerosis in responders and non-responders to fampridine treatment

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**HYPOTHESIS:** Persons with multiple sclerosis (PwMS), already established as responders or non-responders to Fampridine treatment, were compared in terms of disability measures, physical and cognitive performance tests, neurophysiology, and magnetic resonance imaging (MRI) outcomes in a 1-year explorative longitudinal study.

**METHODS:** Data from a 1-year longitudinal study were analyzed. Examinations consisted of the timed 25-foot walk test (T25FW), six spot step test (SSST), nine-hole peg test (9-HPT), five times sit-to-stand test (5-STS), symbol digit modalities test (SDMT), transcranial magnetic stimulation (TMS) elicited motor evoked potentials (MEP) examining central motor conduction times (CMCT), peripheral motor conduction times (PMCT) and their amplitudes, electroneuronography (ENG) of the lower extremities, and MRI measures consisting of brain volume, lesion load, and number of T2-weighted lesions.

**RESULTS:** 41 responders and 8 non-responders to Fampridine were examined in the Region of Southern Denmark. There were no intergroup differences except for the PMCT, where non-responders had prolonged conduction times compared to responders to Fampridine treatment ($p < 0.006$). SSST was associated with CMCT in the total study population throughout the study. After 1 year, CMCT was further prolonged and MEP amplitudes decreased in both groups ($p < 0.05$), while PMCT and ENG measured did not change. Throughout the study, CMCT was associated with the expanded disability status scale (EDSS), and 12-item multiple sclerosis walking scale (MSWS-12), while SDMT was associated with MRI findings of lesion load, lesion load normalized to brain volume, and number of T2-weighted lesions.

**DISCUSSION:** PMCT is prolonged in non-responders to Fampridine treatment when compared to responders. TMS-elicited MEPs and the SDMT can be utilized as markers of disability progression and lesion activity visualized by MRI, respectively.

DAREMUS

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