

electrical resistance (TEER) value in the BMECs, with the presence or absence of recombinant human sRAGE (rhsRAGE)

Results: Serum levels of sRAGE in NMO patients were found to be significantly lower compared to those in HCs. Levels of sRAGE have positive relationship with EDSS, protein levels of CSF and CSF/serum albumin ratio. NMO sera significantly decreased TEER values in the BMECs as compared with HCs. Treatment with rhsRAGE attenuated the reduction of TEER values induced by NMO sera.

Conclusion: The significant reduction of sRAGE in NMO patients relative to HCs indicates the potential role for RAGE axis in NMO clinical pathology. The levels of sRAGE may be associated with clinical severity and disruption of blood-brain barrier in NMO. Blocking the RAGE signals by rhsRAGE may be a new treatment target against NMO.

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SHIFT 6 - MS & DEMYELINATING DISEASES

The incidence of multiple sclerosis in Danish women has duplicated over the last sixty years

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Background: Incidence of multiple sclerosis (MS) has increased in the western world over several decades probably caused by increasing exposure to environmental risk factors.

Objective: To analyse the development of the nationwide incidence rates of MS in men and women in Denmark since 1950.

Patients and Methods/Material and Methods: Since 1950 data on virtually all patients with onset of MS in Denmark have been recorded in the nationwide Danish Multiple Sclerosis Registry, which has been notified by all Danish departments of Neurology, MS clinics, and MS rehabilitation hospitals. This has enabled monitoring of MS incidence in Denmark over six decades.

Results: We have registered 19,378 cases with clinical onset of confirmed MS from 1950 to 2009. From the 1950-1959- to the 2000-2009-onset period incidence more than doubled in women with an increase from 5.95 (95% CI: 5.63-6.28) to 12.12 (95% CI: 11.70-12.55) compared with a modest 24% increase in men from 4.49 (95% CI: 4.21-4.78) to 5.58 (95% CI: 5.30-5.87). Accordingly, the Female: Male sex ratio increased from 1.32 to 2.08. Based on the 2000-2009-onset period, we estimated the cumulative lifetime risk of MS at 0.87% in women and 0.40% in men.

Conclusion: The incidence of MS has doubled in women and only modestly increased in men over the last 60 years. The low increase of MS incidence in men indicates that better case ascertainment cannot account for the marked increase in women. Lifestyle changes in women like fewer childbirths, increased occurrence of obesity, and increased cigarette consumption may be the culprits.

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SHIFT 6 - MS & DEMYELINATING DISEASES

Biotin-deficiency and lower biotin ranges in MS patients- where is the connection?

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Background: After further studies 2016 confirmed effects of high dose biotin in chronic MS the question arose, if biotin deficiency is frequent in MS. Low biotin levels are rare. Biotin is synthesized by intestinal bacteria in amounts, comparable to nutritional intake. Anagnostouli (1999) first reported lower values for biotin in CSF and serum in MS. It could be argued, that biotin deficiency is a risk factor for MS because biotin is an limiting coenzyme in fatty acid synthesis. In the present study we tested if low biotin levels are more frequent in MS and therefore might prove to be a risk factor for onset of the disease and a interesting biomarker for microbiom diversity.

Objective: Blood serum can be tested easily to evaluate biotin levels. Levels with 100-200 ng/l are suboptimal, lower than 100 ng/l require substitution.

Patients and Methods/Material and Methods: Biotin serum levels from 146 MS-patients, and a control group with 82 patients were checked (Elisa).

Results: In 58,5 % we found normal ranges, in 28,7% suboptimal ranges, 12,8% had ranges under 100 ng/l. The average biotin range in 146 MS patients was 260,9, median 222,5, in the control group 335, median 278 with a significant difference ($p < 0,001$).

Conclusion: These findings suggest a high probability of lower biotin levels in MS patients. As a limiting coenzyme for myelin synthesis and mitochondrial function low biotin levels might be a risk factor for MS. As biotin substitution is a simple and low cost procedure, further investigations should prove the therapeutic potential of biotin supplementation in MS.

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SHIFT 6 - MS & DEMYELINATING DISEASES

Prevalence of leptomeningeal foci of gadolinium enhancement in multiple sclerosis and its relationship to the disease severity

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Background: Leptomeningeal contrast-enhancement (LM CE) on post-contrast Fluid attenuation inversion recovery (FLAIR) magnetic-resonance imaging (MRI) sequence has been associated with disease severity and brain atrophy in multiple sclerosis (MS), but there is still a need for more evidence.

Objective: The aim of this study was to assess the prevalence of LM CE and its relationship to disease severity.

Patients and Methods/Material and Methods: Institutional Review Board (IRB) approval was received, all patients consented for the study. LM CE was detected on post-contrast 3D FLAIR sequence. Expanded Disability Status scale (EDSS) score, number of relapses during 5 years from MS onset and number of contrast-enhancing lesions on T1 weighted images were counted.

Results: 54 patients with MS were included into this study. The median (IQR) age and disease duration were as follows: 42 (22.5)

years, 86 (149.05) months, respectively. LM CE was detected in 22/54 (41%) patients. The median disease duration and EDSS score were higher in LM CE positive subgroup (111 vs. 70.5 months, $p=0.0098$; 4.0 vs 3.75, $p=0.039$, respectively). However, the median number of relapses during 1 and 5 years from the disease onset didn't differ between LM CE positive and negative patients ($p=0.2362$; $p=0.091$, respectively). Both groups had similar prevalence of T1 Gd-enhancing lesions ($p=0.5306$). No difference in the median T1 Gd-enhancing lesions count was revealed ($p=0.3842$).

Conclusion: LM CE is a feasible biomarker, associated with longer disease duration and higher disability, but equal relapse rate, that may point towards possible neurodegeneration pathways.

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SHIFT 6 - MS & DEMYELINATING DISEASES

Basic immunological profile changes of secondary progressive multiple sclerosis patients treated with BAF312 (SIPONIMOD)

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Background: The ongoing Phase III EXPAND trial is a multicenter, randomized, double-blind, placebo-controlled study comparing the efficacy and safety of BAF312 to placebo in patients with SPMS. BAF312 (Siponimod) is a new sphingosine 1-phosphate receptor agonist which selectively modulates the sphingosine 1-phosphate receptor (S1P_{1,5}).

Objective: To evaluate immunological profile changes of secondary progressive multiple sclerosis (SPMS) patients before, at 6 months and 12 months post-BAF312 treatment.

Patients and Methods/Material and Methods: Sponsored by NIH NIAID Autoimmune Center of Excellence (ACE), a subset of SPMS patients in the EXPAND trial were recruited for the AMS04 study. PBMCs were isolated from the patients before and after 6 months (6M) and 12 months (12M) of treatment; immunological profile changes were obtained from flow cytometry.

Results: The BAF312 treated group has a significantly lower percentage of CD4⁺ T cells (Mean \pm SD: 3.4 ± 1.7 at 6M and 4.3 ± 4.2 at 12M) compared to the placebo-treated group. However, the percentage of CD8⁺ T cells did not change significantly. Percentage of B lymphocytes was also significantly reduced (Mean \pm SD: 1.4 ± 1.2 at 6M and 1.3 ± 0.9 at 12M), while percentage of monocytes and NK cells were significantly increased with BAF312 treatment compared to placebo group.

Conclusion: BAF312 treatment in SPMS decreased the percentage of CD4⁺ T and B cells, with relative enrichment of monocyte and NK cells. Our longitudinal study will allow us to determine the relationship of these changes to disease progression.

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SHIFT 6 - MS & DEMYELINATING DISEASES

Accuracy of edss and SDMT in the detection of disease activity: Real-world clinical practice results

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Background: Relapse rate and changes in MRI and the Expanded Disability Status Scale (EDSS) are universally used as indicators of therapeutic efficacy in disease modifying treatments in multiple sclerosis (MS). Though, the EDSS has limitations, namely, in the assessment of cognitive dysfunction.

Objective: To investigate the accuracy of clinical measures in the detection of disease activity.

Patients and Methods/Material and Methods: Patients with RRMS were evaluated using clinical and MRI measures in two different moments. Disease activity was defined as >1 relapses and/or changes in MRI (≥ 2 Gd-enhancing or new T2 lesions). It was considered a change ("clinically meaningful worsening") if EDSS > 1, Timed 25-foot walk (T25FW) > 20%, 9-hole peg test (9HPT) > 20%, and symbol digit modality test (SDMT) > 10%. Classification accuracy statistics and Fisher's exact were applied.

Results: Of the 127 patients included (age = 42 ± 11 , education = 14 ± 7 , disease duration = 11.5 ± 7 years; first evaluation EDSS = 2.6 ± 3.4 , and time between evaluations = 12 ± 5 months), 41 (32%) met the criteria for disease activity. Changes in EDSS and SDMT correctly classified (sensitivity) respectively 22/41 (54%) and 24/41 (59%) patients with disease activity. However, there was a modest association between changes in EDSS and SDMT ($p=0.034$; 30/127 patients had changes in one measure but not on the other). When combined, the sensitivity of EDSS and SDMT reached 93%. Both clinical measures correctly classified all patients without disease activity (specificity). The sensitivity of changes in T25FW (15%) and 9HPT (7%) was low.

Conclusion: Changes in EDSS and SDMT have high accuracy in the detection of disease activity. Though, these clinical measures may be sensitive to different aspects of disease activity.

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SHIFT 6 - MS & DEMYELINATING DISEASES

Treatment satisfaction in patients with RRMS treated with teriflunomide in routine clinical practice: Aubpro study design

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Background: Teriflunomide is a once-daily immunomodulator approved for the treatment of patients with relapsing-remitting MS (RRMS).

Objective: To describe the design of AubPRO, a prospective observational study to evaluate treatment satisfaction using patient-reported outcomes (PROs) in patients with RRMS treated with teriflunomide (AUBAGIO®) in routine clinical practice in Australia.

Patients and Methods/Material and Methods: AubPRO will include ~150 adult patients with RRMS initiating treatment with teriflunomide according to local clinical practice. Patients will provide signed informed consent. Study duration for each patient will be ~13 months. The primary