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Background: Several primary progressive multiple sclerosis (PPMS) natural history studies have emonstrated a large degree of heterogeneity in time from disease onset to high levels of disability.

Objective: We aimed to investigate the heterogeneity of long-term disability accumulation in a cohort of PPMS patients and to determine if there are differences between the trajectories of PPMS adjusting for sex.

Methods: All PPMS patients enrolled in RelevarEM registry who had $\geqslant 2$ Expanded Disability Status Scale (EDSS) score, were included in the analysis. A linear mixed model was used to model longitudinal EDSS scores. The best model (lower values better fit) was selected according to both Akaike Information Criterion and Bayesian Information Criterion fit indices and also to parsimony and clinical interpretability of the data. The same indices were used to determine which time function (linear, quadratic, square root, logarithm) best fit the EDSS trajectories over time. Fractional polynomials were used to obtain the best longitudinal fit of the dependent variable (EDSS). The root mean square errors were also calculated.

Results: A total of 125 patients with longitudinal data were included (median observations/patients was 3 (2-5). Mean age at onset of PPMS was 41 years ($\pm$ 11), and mean PPMS duration was 11 years $\pm$ 5.9. The male/female ratio was 1.4. Baseline EDSS was 2.97 ($\pm$1.16) in women and 3.11 ($\pm$1.20) in men, ($p = 0.50$); last EDSS was 5.66 ($\pm$1.56) in women and 6.06 ($\pm$1.56) in men ($p = 0.155$). The mean follow-up time was 10 years ($\pm$5.11) in women and 12.8 ($\pm$6.49) in men ($p < 0.001$). We found high heterogeneity between individuals (intraclass coefficient 43%), suggesting the usual clinical and radiologic variables are not enough to explain the variability in disability accumulation trajectories. We did not observe differences in disability trajectories stratified by sex, adjusted for potential confounders.

Conclusion: A high heterogeneity was found in the trajectory between individuals regarding disability accumulation. We have not found differences stratified by sex. As previously reported, there is a high variability between individuals that cannot be explained by the prognostic markers that we currently have.

Disclosure

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Prevalence of motor and cognitive fatigability in progressive multiple sclerosis and related factors

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Introduction: A progressive MS (PMS) type is a negative prognostic factor for clinical outcomes. The majority of people with PMS present motor (e.g. walking) and cognitive impairments while also reporting fatigue. Objectively, fatigue can be measured by the capacity to sustain a motor or cognitive task which is termed fatigability. Currently, the prevalence of fatigability in PMS is unknown, as well as potential explanatory factors.

Objectives: To investigate the prevalence of walking and cognitive fatigability in PMS and to explore potential explanatory factors in a large sample of PMS patients with cognitive impairments.

Methods: this study analysed baseline data from the CogEx trial, including 298 PMS patients collected across 11 sites in Europe and North America. Inclusion criteria: diagnosis of PMS, 25-65 years old, Expanded Disability Status Scale$<$7, 1.28 SD or more below normative data for the symbol digit modality test (SDMT). Measures, cognitive: Brief International Cognitive Assessment in MS; physical: cardiorespiratory fitness, 6-minute walk test (6MWT) and physical activity (MVPA); Patient reported outcomes (PRO's): hospital anxiety depression scale (HADS), modified fatigue impact scale (MFIS), MS impact scale (MSIS-29), MS walk scale (MSWS-12). For walking fatigability (WF) the distance walk index (DWI$\leqslant$-10%) comparing distance at last and first minute during the 6MWT was used. Cognitive fatigability (CF), $\geqslant$10% decline in the SDMT (last 30sec compared to the first 30sec).

Results: Of 298 participants (83 PPMS, 215 SPMS), 153 (51%) presented WF (DWI=-28.9$\pm$22.1%) and 196 (66%) presented CF (-29.7$\pm$15%). Clinical outcomes were different between patients with *vs* without WF (EDSS=6.0 *vs* 5.0; disease duration=15.7 *vs* 12.9; SPMS, n=124 *vs* 91; use of assistive device, n=115*vs* 72). Patients with WF, presented higher scores of MSIS-29 physical, MFIS total and physical, and MSWS-12, and reduced 6MWT distance, cardiorespiratory fitness and physical activity. Patients with CF showed lower MSIS-29 physical and MFIS psychosocial than non-CF group. Cognitive functions were not different across motor or cognitive fatigability groups.

Conclusions: Half of the cognitively impaired PMS population presented WF which was related to overall higher disability, physical functions and fatigue. Two thirds of PMS showed CF which was not related to overall disability, physical and cognitive functions.

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Nancy D. Chiaravalloti is on an Advisory Board for Akili Interactive and is a member of the Editorial Boards of Multiple Sclerosis Journal and Frontiers in NeuroTrauma.

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Peter Feys is editorial board member of NNR, MSJ and Frontiers in Rehabilitation Sciences, provides consultancy to NeuroCompass and was board of advisory board meetings for BIOGEN.

Clinical aspects of MS - Natural course

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Characterization of the familial multiple sclerosis population in Israel

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Background: While most Multiple Sclerosis (MS) cases are sporadic (SMS), MS may cluster in families, a phenomenon known as familial MS (FMS), possibly due to aggregation of genetic, epigenetic and environmental factors. To date, no study, to the best of our knowledge, has characterised FMS in the Israeli population. Our hypothesis was that demographic and clinical features may differ between FMS and SMS.
Methods: In a retrospective study of 102 patients with FMS and 516 patients with SMS attending our clinic, ethnicity and gender distribution was compared. In a sub-cohort of 76 FMS and 76 SMS patients, matched for age, gender, ethnicity and disease course, clinical aspects were compared.
Results: In the total cohort, females comprised 75% of FMS and 67% of SMS patients. There was a significant difference in ethnic distribution between FMS and SMS; 54.9%, 21.6%, 15.7%, 6.9%, 1% and 73.8%, 16.1%, 5.2%, 2.3%, 2.1% for Jews, Muslims, Christian Arabs, Druze and others, respectively (p=0.00041). In the matched cohort, age at disease onset or diagnosis, frequency of positive oligoclonal bands (OCB) and comorbidity of other autoimmune diseases was comparable, with Hypothyroidism as most frequent comorbidity occurring in 7.9% of FMS and 10.5% of SMS. Most frequent symptom at disease onset was sensory disturbances in both groups, but significantly more in FMS (53% vs. 36%, p=0.024). Relapse rates throughout 15 years were comparable. 33% and 26% of FMS and SMS patients, respectively, had a progressive disease course (relapsing-progressive or secondary-progressive). MS Severity Score was higher in FMS (3.73 vs. 2.98, p=0.033), and Expanded Disability Status Scale tended to be significantly higher throughout 15 years following diagnosis, compared to SMS.
Conclusions: The proportion of Arab ethnicities among FMS is higher compared to among SMS, especially that of Christian Arabs, which is also higher compared to their frequency in northern Israel, where the clinic resides, and beyond our previous observation in the general MS population in Israel.
In comparison to SMS patients, disease progression and disability accumulation are faster in patients
with FMS.

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P455
Clinical and radiological concordance in sibling pairs with multiple sclerosis

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Introduction: Familial forms of Multiple Sclerosis (MS) represent 12.6% of all cases. However, little is known about intrafamilial concordance in both clinical and radiological phenotypes. To this day, most studies on this subject are limited to demographic data or general disability scores such as EDSS.
Objective: The goal of this study is to identify clinical and radiological correlations between siblings with MS.
Aim: To improve the understanding of familial forms of MS and to guide familial counseling for co-affected siblings.
Methods: 31 pairs of siblings in which both individuals have MS have been included. Each patient (n=62) received a comprehensive neuropsychological evaluation, clinical examination, and medical history assessment. Furthermore, a volumetric 3T MRI analysis was performed to quantify key volumes: whole grey matter, cortical grey matter, thalamic volume, and white matter T2-lesions. The identification of correlations between siblings is based on discordance ratio (r = pairwise mean absolute