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Clinical, neuropsychological, immunopathological and radiological analysis of progressive multiple sclerosis patients

Aim of the study

- The study represents a complex longitudinal assessment of patients with primary progressive (PP) and secondary progressive (SP) multiple sclerosis (MS) including clinical and neuropsychological characteristics, as well as immunopathological and neuroimaging biomarkers
- Based on the multifactorial analysis, diagnostic algorithms will be proposed. These may allow for earlier diagnosis of the progressive phase of the disease, and thus enable to earlier optimize the therapy and consequently contribute to the improvement of the therapeutic effect in progressive MS patients
- Outcomes of this study may also contribute to the refinement of the methodology of the evaluation of disease progression and assessment of the efficacy of the therapies used in PMS

Methods

1. **Study design** – PPMS and SPMS patients were prospectively recruited in the Department of Neurology, Medical University of Lodz. Study measurements and analyses were performed at two consecutive time points: (1) at the study entrance (Baseline) and (2) after 12 months (Follow-up). The study design and all the study procedures received the approval of the Local Bioethics Committee of the Medical University of Lodz (No. RNN/128/20/KE and KE/564/23)
2. **Clinical analysis** – medical history, neurological examination and Expanded Disability Status Scale (EDSS)
3. **Neuropsychological analysis** – BICAMS battery consisting of Symbol Digit Modalities Test (SDMT), California Verbal Learning Test (CVLT) and Brief Visuospatial Memory Test Revised (BVMT-R); Verbal Fluency Test (VFT), The Stroop Color and Word Test (SCWT)
4. **Laboratory analysis** – concentrations of neurofilament light chains (NfL), chemokine ligand 13 (CXCL-13) and chitinase-3 like-protein-1 (YKL-40) were measured in serum with enzyme linked immunosorbent assay (ELISA)
5. **Radiological analysis** – volumetric parameters of local brain atrophy were assessed on MRI scans with the application of machine learning software; measurements included i.a.: thalamic, cerebellar, hippocampal and corpus callosum volumes (see examples below – Figure 3.)

Parameter	Whole group	PPMS	SPMS	p-value
Age [years]	55,17±8,21	54,70±8,65	55,63±7,92	0,7899
Sex [female - F, male - M]	33 F, 14 M	17 F, 6 M	16 F, 8 M	0,5871
Years of education [years]	12,76±3,17	13,14±3,47	12,42±2,90	0,5958
Disease duration [years]	14,19±9,31	8,30±6,85	19,83±7,79	**<0,0001**
Years from diagnosis [years]	10,04±8,81	4,78±5,74	15,08±8,33	**<0,0001**

Table 1. Baseline characteristics of the study group. Data shown as means with standard deviation.

Parameter	Whole group		PPMS		SPMS	
BICAMS	R	p-value	R	p-value	R	p-value
BICAMS baseline & NfL baseline	-0,16	0,3080	-0,37	0,1123	0,02	0,9378
BICAMS baseline & CXCL-13 baseline	0,13	0,3962	0,14	0,5527	0,15	0,4897
BICAMS baseline & YKL-40 baseline	-0,11	0,4602	-0,24	0,3012	0,01	0,9758
BICAMS follow-up & NfL follow-up	0,01	0,9519	-0,51	0,1567	0,38	0,1774
BICAMS follow-up & CXCL-13 follow-up	-0,11	0,6184	-0,29	0,4448	-0,09	0,7643
BICAMS follow-up & YKL-40 follow-up	0,21	0,3456	**0,67**	**0,0466**	-0,26	0,3745

Table 2. Correlations between BICAMS scores and biomarkers serum levels at baseline and after follow-up period with regard to PMS subtype.

SPMS	AUC	SE	p-value
NfL	0,82	0,11	**0,0043**
CXCL-13	0,53	0,15	0,8244
YKL-40	0,80	0,12	**0,0093**
BICAMS	0,90	0,08	**0,0000**
BVMT-R sum	0,68	0,15	0,2505
CVLT	0,85	0,10	**0,0004**
SDMT	0,88	0,09	**0,0001**
SCWT A	0,52	0,15	0,9110
SCWT B	0,77	0,13	**0,0371**

Table 3. Prediction models of progression of physical disability in SPMS group.

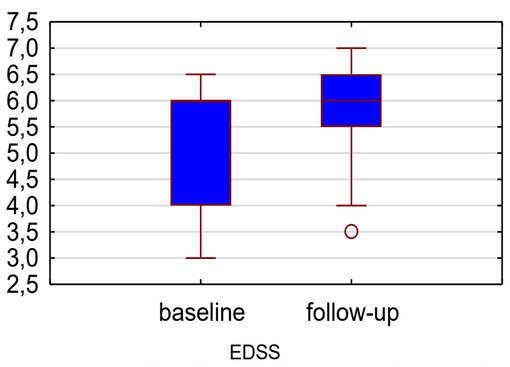


Figure 1. Significant increase in median EDSS score during follow-up period in the whole study group, p=0,0464.

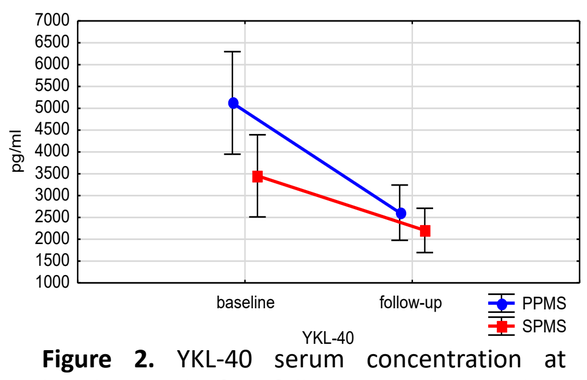


Figure 2. YKL-40 serum concentration at baseline and after follow-up with regard to PMS subtype, p=0,0007 (whole group), p=0,0019 (PPMS), p=0,0613 (SPMS).

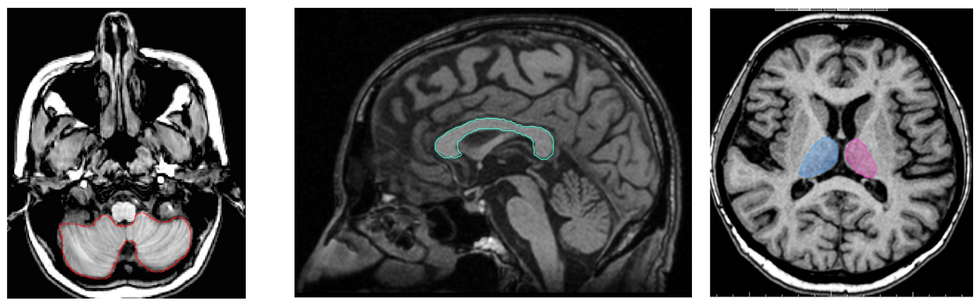


Figure 3. Examples of brain MRI measurements – volumes of cerebellum, corpus callosum, thalami.

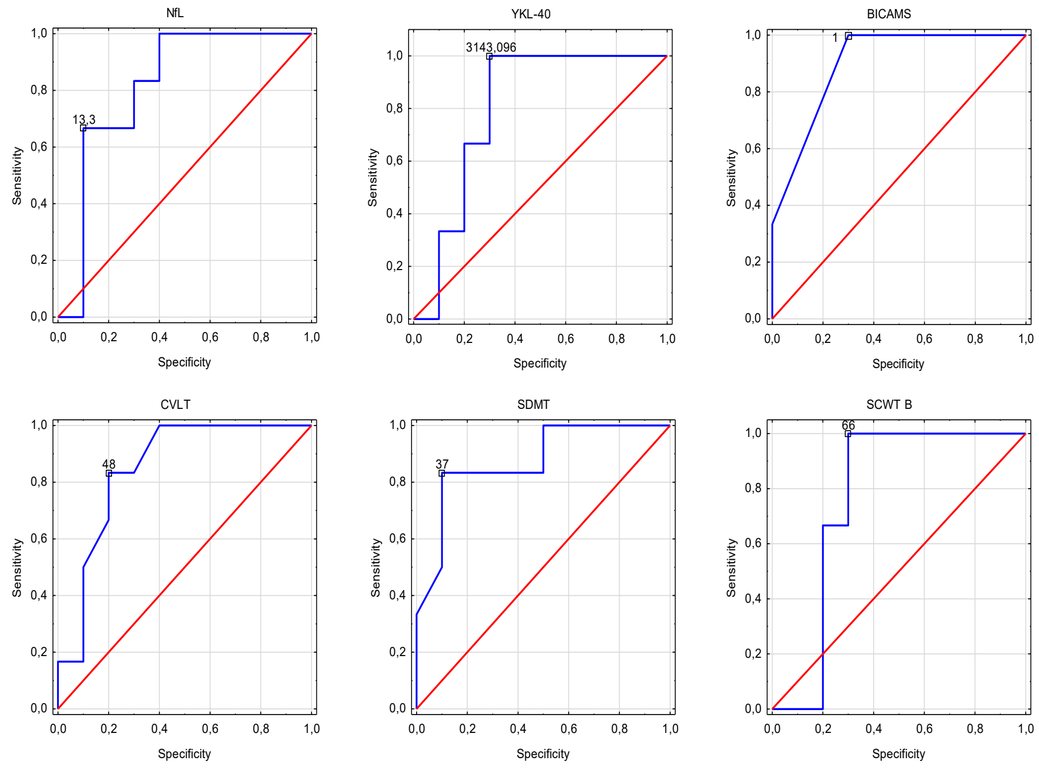


Figure 4. Prediction models of 0,5 point increase in EDSS with regard to molecular biomarkers and neuropsychological tests in SPMS subgroup. Only data with p<0,05 is shown.

Results

- Fifty (50) progressive MS patients have been enrolled in the study (n=25 PPMS and n=25 SPMS patients). Follow-up examinations (collection of clinical data, MRI examinations, laboratory and neuropsychological analysis) were performed in n=44 patients (n=6 patients discontinued the study before the Follow-up examination due to personal reasons)
- The results of the interim analysis of 47 Baseline and 23 Follow-up measurements available at the moment of poster submission (30.04.2024) are presented above
- There were no differences between PPMS and SPMS groups in basic demographic parameters (medium age, sex distribution, years of education), however, at the study entrance, both disease duration and time from MS diagnosis were significantly higher in SPMS group (Table 1.)
- Neurological disability assessed in EDSS increased significantly at Follow-up in the whole group of progressive MS patients (Figure 1)
- In the analysis of molecular biomarkers, a significant decrease of YKL-40 serum level in PPMS patients was observed at Follow-up (Figure 2.). At the same time a significant increase in CXCL-13 serum concentration in SPMS group was noted (data not shown)
- The analysis of the correlations between molecular markers and neuropsychological parameters is presented in Table 2. and Table 3.
- Figure 4. presents prediction models of neurological disability progression based on the parameters investigated in the study

Conclusions

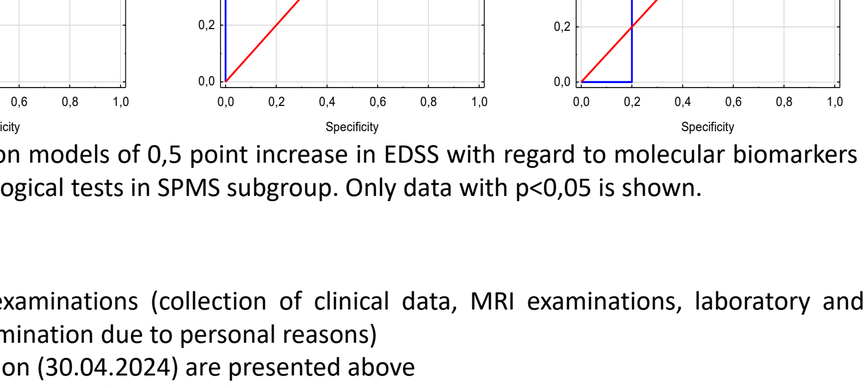
The interim analysis of the study outcomes indicates an existence of complex differences between SPMS and PPMS patients, which may be helpful in better prediction of the disease course and treatment planning in those patient groups. Importantly, the successful prognostic algorithms need to be based on multiple factors encompassing diverse categories i.e. clinical, molecular and radiological parameters.

Publications

1. First authorship, review article **"Symbol Digit Modalities Test in progressive multiple sclerosis"**, *Polish Journal of Neurology and Neurosurgery,* IF=2.9 and 100 ministerial points
2. First authorship, original article **"Serum biomarkers and cognitive profile in progressive multiple sclerosis patients may help predict disease progression - a longitudinal study"** – under submission
3. First authorship, original article **"MRI volumetric parameters of brain atrophy, serum biomarkers and cognition in progressive multiple sclerosis patients - a longitudinal study"** – under submission

Additional publication achievements:

1. First authorship, case report article **"A loop that matters - an unusual case of Bow Hunter's Syndrome"**, *Brain Sciences*, IF=3.706 and 100 ministerial points
2. Co-authorship, original article **"Physical Activity, body Composition, serum myokines and the risk of death in hemodialysis patients"**, *Medicina*, IF=2.6 and 40 ministerial points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