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Serum NSE level and disability progression in multiple sclerosis ☆

Marcus W. Koch [a,b,*], Suzanne George [a], Winona Wall [a], V. Wee Yong [a], Luanne M. Metz [a]

[a] Department of Clinical Neurosciences and Hotchkiss Brain Institute, University of Calgary, Calgary, Alberta, Canada
[b] Department of Community Health Sciences, University of Calgary, Calgary, Alberta, Canada

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ABSTRACT

Background: : Previous studies suggested that serum neuron specific enolase (NSE) may be a biomarker associated with progression in MS.
Methods: : We measured serum NSE levels in 385 patients with multiple sclerosis (MS) (264 with relapsing–remitting (RR) MS, 86 with secondary progressive (SP) MS, and 35 with primary progressive (PP) MS), and compared levels between disease courses, between users and non-users of immunomodulatory treatment, and between patients with worsening or stable disability at one year follow-up (available in 161 patients). We also investigated the correlation between serum NSE and Expanded Disability Status Scale (EDSS) and MS Severity Score (MSSS) scores in the whole cohort and in subgroups, and built a multiple linear regression model to assess the influence of predictor variables on serum NSE.
Results: : Age was the only independent predictor of serum NSE levels in the multiple linear regression model. In the subgroup of patients with PPMS, there was a moderate correlation between serum NSE and increasing MSSS (Pearson's r 0.35, $p = 0.04$) and EDSS (Spearman's rho 0.37, $p = 0.03$) scores.
Conclusion: : Our data do not support the use of serum NSE as a prognostic biomarker in RRMS or SPMS. The correlations of serum NSE with EDSS and MSSS in the PPMS subgroup are interesting, but based on a small sample size and require replication in other cohorts.

1. Introduction

Multiple sclerosis (MS) is an inflammatory and neurodegenerative disease of the central nervous system (CNS) with unknown cause [1]. The disease course of MS varies widely between individual patients, and one of the most consistent findings in natural history studies of the disease is the wide variety in disease severity, or the time taken to landmark disability scores [2]. While some factors, such as the age at disease onset and relapsing–remitting versus primary progressive disease course are associated with disability accumulation, it remains very difficult to predict the prognosis of MS in an individual patient [2].

The search for sensitive biomarkers that predict the disease course is currently an active area of research [3]. Such biomarkers could be used to predict the overall prognosis for patient counseling and to select patients at highest risk for a severe disease course for more aggressive treatment. An additional important use for biomarkers is as outcome measures in phase 2 trials for new treatments for MS, which currently rely on imaging and clinical outcome measures alone.

Despite much research, sensitive biomarkers predicting the disease course of MS are currently lacking. Several previous studies have investigated the protein biomarker Neuron Specific Enolase (NSE) in MS [4–7]. NSE is an important enzyme for glycolysis that is most commonly expressed in neurons, and it was hypothesized that levels of NSE in the cerebrospinal fluid (CSF) or serum could be used as a marker of neuronal degeneration [8]. The underlying reasoning here was that high levels of NSE would be associated with high levels of neuronal death and subsequent secretion of NSE into CSF or serum, or alternatively that low levels of NSE would be a reflection of an overall reduced pool of neurons in the CNS. Previous studies on NSE levels in MS were relatively small in size and most often lacked follow-up of clinical outcomes. Here we present our findings on the association of serum NSE levels and disability accumulation in a large cohort of patients with MS.

2. Methods

2.1. Study participants and clinical data

Data for this study were collected in a large longitudinal study that enrolled patients from the Calgary MS clinic. The Calgary MS clinic is the main care centre for patients with MS in the southern part of the province of Alberta in Canada. Patients had a diagnosis of MS according to the Poser [9] or McDonald [10] diagnostic criteria. Expanded Disability Status Scale (EDSS) [11] scores and disease course were recorded by

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* Corresponding author at: Department of Clinical Neurosciences and Hotchkiss Brain Institute, University of Calgary, Calgary, Alberta, Canada. Tel.: +1 403 944 2509; fax: +1 403 270 7162.
E-mail address: mwkoch@ucalgary.ca (M.W. Koch).

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an MS neurologist at the Calgary MS clinic. Venous blood samples were drawn through venipuncture in the antecubital fossa at the MS clinic on the same day, and the serum was separated through centrifugation. The samples were inspected and hemolytic samples were discarded. The serum samples were stored at −80 °C until analysis.

The Multiple Sclerosis Severity Score (MSSS) [12] is a general measure of the speed of disability accumulation, based on a very large patient cohort drawn from several natural history cohorts. An MSSS score of above 5.0 denotes higher than average speed of disability accumulation. We calculated MSSS scores at baseline according to the method proposed by Roxburgh and colleagues [12]. One year follow-up data were obtained from the MS clinic database. We defined clinic visits that fell between 11 and 13 months after the date of the serum sample as one year follow-up visits. The study was approved by the University of Calgary Research Ethics Board. Informed consent was received from all participants.

2.2. NSE measurement

NSE levels were measured in the serum samples with a commercially available ELISA kit (Human Enolase 2/Neuron-specific Enolase Quantikine ELISA Kit, R&D systems, Minneapolis, Minnesota, United States of America) according to the manufacturer's instructions.

2.3. Statistical analysis

The difference in NSE levels between patients with an EDSS score of below 6.0 and 6.0 and higher at baseline, between patients with increased and stable EDSS at one year follow-up, and between patients using and not using an immunomodulatory drug (IMD) were analyzed with Student's *t* test. We compared NSE levels between RRMS, SPMS and PPMS, and between five groups of patients grouped by change in their follow-up EDSS score (1.0 or more lower, 0.5 points lower, no change, 0.5 point increase, 1.0 point increase compared to baseline) with the Kruskal–Wallis test. If the Kruskal–Wallis test showed a significant difference between the groups overall, it was followed by Dunnett's post test for pairwise comparisons between subgroups. The correlation between serum NSE levels and EDSS and MSSS scores was analyzed with Spearman's rank correlation test and Pearson's correlation test, respectively.

We built a multiple linear regression model to estimate the effect of predictor variables on serum NSE levels. In this model serum NSE was the dependent variable, and age, sex disease duration, disease course EDSS at baseline and IMD use were entered as independent predictor variables. Statistical significance was taken to be at the two-sided 0.05 level. All statistical analyses were performed with the R statistical software package for Windows, version 3.0.1 [13].

3. Results

3.1. Patient characteristics

Patient characteristics at baseline and at one year follow-up are shown in Table 1. We included 385 patients with MS, 302 women and 83 men. Of the 385 patients, 264 had relapsing–remitting MS (RRMS), 86 had secondary progressive MS (SPMS), and 35 had primary progressive MS (PPMS). The baseline EDSS score was 6.0 or higher in 120 patients, and lower than 6.0 in 265 patients. The baseline MSSS score was higher than 5.0 in 159 patients, and 5.0 or lower in 226 patients. Of the 350 patients with either RRMS or SPMS, 204 were using an IMD; 115 were using glatiramer acetate, 88 were using interferon beta, and one patient was using mitoxantrone. None of the patients with PPMS were using an IMD.

One year follow-up data was available for 161 patients 129 women and 32 men. Of these patients, 127 had RRMS, 21 SPMS, and 13 had PPMS. The EDSS at one year follow-up was increased compared to baseline in 49 patients, and unchanged or lower in 112 patients. For further analyses, we divided patients into five groups according to the change in EDSS score at followup: 1.0 points or more lower (n = 10), 0.5 points lower (n = 18), unchanged (n = 84), 0.5 points higher (n = 24), and 1.0 points or higher (n = 25).

Table 1
Patient characteristics at baseline and at one year follow-up.

	Overall	RRMS	SPMS	PPMS
Baseline				
n	385	264	86	35
Sex: female/male	302/83	213/51	69/17	20/15
Age (median, IQR)	47, 40–54	45, 38–50	53, 47–57.75	52, 47.5–59
Disease duration (median, IQR)	11, 6–19	9, 5.75–16	18, 12.25–24.75	11, 5–17.5
EDSS (median, IQR)	3.0, 2.0–6.0	2.5, 1.5–3.5	6.5, 6.0–6.5	6.0, 4.0–6.5
MSSS (mean, SD)	4.44, 2.58	3.47, 2.13	6.4, 2.17	6.95, 2.16
Serum NSE level [μg/L] (mean, SD)	2.83, 0.75	2.78, 0.7	2.87, 0.79	3.15, 0.98
One year follow-up				
n	161	127	21	13
Sex: female/male	129/32	107/20	14/7	8/5
Age (median, IQR)	48, 41–54	46, 40–51	51, 46–56	54, 49–64
Disease duration (median, IQR)	11, 7–18	11, 7–17	14, 8–20	8, 7–17
EDSS (median, IQR)	3.0, 2.0–6.0	2.5, 2.0–4.25	6.5, 6.0–6.5	6.0, 4.0–6.5
Number EDSS increased/stable	49/112	39/88	8/13	2/11

IQR: interquartile range, SD: standard deviation.

3.2. NSE levels

The results of the group comparisons at baseline and one year follow-up are shown in Table 2. Serum NSE levels were increased in SPMS compared with the RRMS and in the PPMS compared with SPMS, with an overall significant difference between the groups (Kruskal–Wallis p = 0.04, Table 2). Dunnett's post hoc test for pairwise comparisons showed a significant difference between PPMS and RRMS

Table 2
Comparison of serum NSE levels between different patient groups at baseline and one year follow-up. There is a significant difference in serum NSE levels between the disease courses of MS with levels increasing from RRMS to SPMS to PPMS.

Patient group	n	Serum NSE level (SD) [μg/L]	p
Whole cohort	385	2.83 (0.76)	–
RRMS patients	264	2.78 (0.70)	
SPMS patients	86	2.87 (0.79)	0.04[a]
PPMS patients	35	3.15 (0.98)	
Patients with RRMS or SPMS on IMD	204	2.91 (0.73)	0.02[a]
Patients with RRMS or SPMS not on IMD	146	2.72 (0.71)	
EDSS at baseline below 6.0	265	2.79 (0.73)	0.15[b]
EDSS at baseline 6.0 or higher	120	2.92 (0.81)	
MSSS at baseline above 5.0	159	2.8 (0.72)	0.26[b]
MSSS at baseline 5.0 or lower	226	2.89 (0.8)	
All patients with one year follow-up	161	2.8 (0.72)	–
EDSS at one year follow-up increased	49	2.78 (0.76)	0.61[b]
EDSS at one year follow-up unchanged or lower	112	2.84 (0.64)	
EDSS at one year follow-up 1.0 or more lower	10	2.48 (0.63)	
EDSS at one year follow-up 0.5 lower	18	2.75 (1.06)	
EDSS at one year follow-up unchanged	84	2.82 (0.7)	0.28[a]
EDSS at one year follow-up 0.5 higher	24	2.84 (0.76)	
EDSS at one year follow-up 1.0 or more higher	25	2.83 (0.52)	

IMD: immunomodulatory drug, SD: standard deviation.
[a] Kruskal–Wallis test.
[b] *t*-Test.