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Body mass index influence interferon-beta treatment response in multiple sclerosis

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ABSTRACT

Obesity is a possible risk factor of multiple sclerosis (MS), but the association between obesity and MS disease activity has not been explored. In a cohort of 86 MS patients, 80% of overweight or obese patients (BMI ≥ 25 kg/m^2) had MRI activity compared to 48% of the normal-weight patients (BMI < 25 kg/m^2) ($p = 0.001$) during interferon-beta treatment. NEDA-status (no evidence of disease activity) was defined as a composite that consisted of absence of any relapses, sustained disability-progression and MRI-activity. Among normal-weight patients 26% obtained NEDA-status compared to only 13% of patients with BMI >25 ($p = 0.05$). This may indicate that BMI affects interferon-beta treatment response.

1. Introduction

Multiple sclerosis is an autoimmune disease of the central nervous system, caused by an interaction of genetic and environmental risk factors. Some HLA-alleles, low serum vitamin D levels, Epstein–Barr virus infection and smoking are all factors associated with increased MS risk (Sawcer et al., 2014; Ascherio and Munger, 2007). Obesity has also been suggested as a possible risk factor for MS, and during the last decade, several publications have reported an association between higher BMI in youth and early life and MS (Munger et al., 2009, 2013; Hedstrom et al., 2012; Wesnes et al., 2014; Langer-Gould et al., 2013).

Obesity induces a state of low-grade chronic systemic inflammation (Overs et al., 2012). It is a well-known risk factor for multiple conditions including cardiovascular and related metabolic disorders and some

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forms of malignancies, and has also been associated with an unfavorable course of several autoimmune diseases (Versini et al., 2014). Obesity in female MS patients at the time of diagnosis is associated with a relapsing course at disease onset (Marrie et al., 2011). Obesity is also associated with a greater risk of depression, lower functional capacity and worse self-rated health status among MS patients (Taylor et al., 2014; Cambil-Martin et al., 2014). Recently, a positive correlation between BMI and disability evaluated by Expanded Disability Status Scale (EDSS) was reported (Oliveira et al., 2014). So far no study has explored the association between BMI and disease activity, or whether BMI influences the response to interferon-beta (IFNβ)-treatment in RRMS.

The main aim of this study was to explore if BMI has an impact on clinical and MRI disease activity in untreated patients with RRMS and during IFNβ -therapy. Based on the association of BMI with systemic inflammation as well as the role of inflammation and vitamin D status in MS disease progression, we also explored possible associations between BMI and selected inflammatory markers and serum vitamin D.

2. Material and methods

2.1. Study population and design

This was a prospective study of 86 patients with RRMS followed for a total of 24 months with repeated serum analyses, MRI scans and EDSS assessments (Table 1). The patients were included in the original OFAMS-study, a randomized double-blind, placebo-controlled multicenter trial of omega-3 fatty acids including 92 Norwegian patients with RRMS according to the McDonald criteria. The patients were aged 18–55 years with an EDSS score ≤5, and ≥1 relapse or new T1-weighted gadolinium enhancing (T1Gd+) or T2-weighted (T2) lesion on MRI in the year prior to inclusion. They did not receive any immunomodulatory therapy at inclusion and the first 6 months, but thereafter all patients received 44 μg IFNβ subcutaneous injections three times weekly. No effects from ω-3 fatty acids supplementation on MS disease activity were detected, and all patients were therefore pooled in the current analysis (Torkildsen et al., 2012).

2.2. Measurement of inflammation markers and 25-hydroxyvitamin D

Serum samples were collected at baseline and after 1, 3, 6, 7, 9, 12, 18 and 24 months and stored at −80 °C until analysis. 25-hydroxyvitamin D was measured with a radioimmunoassay kit (ImmunoDiagnostic Systems, Boldon, UK). The concentrations of osteoprotegerin (OPG), soluble tumor necrosis factor receptor 1 (sTNFR1), the chemokines CXCL16 and CCL21, transforming growth factor (TGF)β1, pentraxin 3 (PTX3), matrix metalloproteinase 9 (MMP-9), interleukin-1 receptor antagonist (IL-1Ra), osteopontin (OPN), and activated leukocyte cell adhesion molecule (ALCAM) were measured by enzyme immunoassay (EIA) obtained from R&D systems (Stillwaters, MN) as described (Holmoy et al., 2013). The analyses were performed simultaneously for all samples from each patient. For each marker consecutive samples from each patient were analyzed in neighboring wells on the same plate. The lab technicians were blinded for treatment as well as MRI activity. The intra- and inter-assay coefficient of variation were <10% for all EIAs.

Table 1
Clinical, MRI and laboratory measurements during study period.

	Month												
	Baseline	1	2	3	4	5	6	7	8	9	12	18	24
	No treatment							Interferon β1a treatment					
MRI examination	•		•	•	•	•	•	•	•	•	•		•
EDSS evaluation	•						•				•	•	•
Serum-inflammation markers and 25-hydroxyvitamin D	•		•		•		•	•		•	•	•	•

MRI = magnetic resonance imaging; EDSS = Expanded Disability Status Scale. Relapses were recorded throughout the study period.

2.3. HLA-DRB1 typing

The HLA-DRB1 status was determined by DNA sequencing using SeCoreLoc DRB1 SEQ kit (Invitrogen, Carlsbad, CA, USA) at the Department of Immunology, Oslo University Hospital, Rikshospitalet. Patients carrying at least one DRB1*15 allele were considered HLA-DRB1*15 positive.

2.4. Body mass index (BMI)

Height and weight were registered for all patients at inclusion, and BMI was calculated as weight/height^2. The patients were categorized based on the WHO classification of obesity into three groups; Normal weight patients, (BMI < 25 kg/m^2); Overweight patients (BMI 25–30 kg/m^2); Obese patients (BMI > 30 kg/m^2). For some analyses, overweight and obese patients were merged into one group.

2.5. MRI

MRI was performed at baseline, monthly for 9 months and after 12 and 24 months according to a standardized protocol comprising T2-weighted and T1-weighted gadolinium enhancing (T1Gd+) scan using a standard head coil with a 1,5 Tesla MRI unit. Blinded assessments of new T1Gd+ lesions and new or enlarging T2 lesions were conducted by 2 experienced neuroradiologists. The sum of T1Gd+ lesions and new or enlarging T2 lesions was denoted as combined unique activity (CUA).

2.6. Composite score of no evidence of disease activity (NEDA)

NEDA was defined as a composite that consisted of absence of any relapses, no evidence of sustained disability progression and no MRI activity (new T1Gd+ or new/enlarging T2-lesions) on MRI examinations for the given period (Rotstein et al., 2015). A relapse was defined as the appearance of new symptoms or signs that lasted more than 24 h without concurrent fever or illness. Progression was defined as an EDSS score increase of 1 or more recorded at a clinical visit that was sustained at the subsequent clinical visit 6 months later.

2.7. Statistics

MRI activity was dichotomized to 0 (no activity) and 1 (activity) before the analyses. As the distribution of the inflammation markers was skewed, all markers were LN-transformed for the statistical analyses. Data were described as means and standard deviations (SD) or frequencies and percentages, as appropriate.

The association between BMI and MRI activity before and during IFNβ-treatment was assessed by logistic regression model for hierarchical data. The model contained random effects for patients and fixed effects for BMI-categories, dummy identifying before-during IFNβ period and the interaction between the two. The results were presented as odds ratios (ORs) with corresponding 95% confidence intervals (CI) within each BMI category (normal weight group as reference) before and during IFNβ-treatment as well as ORs for decrease in MRI activity from before to during IFNβ-treatment period. The ORs were also adjusted for age and HLA-DRB1*15 status.

The association between continuous BMI and inflammation markers was estimated by a linear mixed model with random effects for patients and fixed effects for BMI. The results were reported as regression coefficients with the corresponding 95% CI. The change in inflammation markers from before to during IFNβ-treatment was compared between two BMI categories by estimating a linear mixed model with random