

Autonomic Nervous System Function in Newly Diagnosed Multiple Sclerosis: Association With Lipid Levels and Insulin Resistance

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Received April 3, 2021

Accepted August 26, 2021

Epub Ahead of Print October 30, 2021

Summary

Autonomic nervous system (ANS) disorders are common in multiple sclerosis (MS). Previous studies showed differences in insulin resistance (IR) and lipoprotein levels in MS subjects compared to controls. Lipolysis caused by increased sympathetic activity could be one of the possible linking mechanisms leading to dyslipidemia in MS. Our study aimed to evaluate ANS activity in the context of glucose and lipid metabolism in people with MS. We prospectively measured short-term heart rate variability (HRV), fasting lipoprotein concentrations, and calculated IR indices based on plasma glucose and insulin levels during oral glucose tolerance test (oGTT) in 32 patients with MS and 29 healthy controls matched for age, sex and body mass index in our study. There was no significant difference in HRV parameters and lipoprotein levels between MS and controls. A significant positive correlation was found between low/high-frequency power ratio (LF/HF) and triglycerides ($r=0.413, p=0.021$) in MS subjects but not in controls. A significantly lower whole-body insulin sensitivity index (ISI_{Mat}) was found in patients with MS compared to the control group (7.3 ± 3.7 vs. $9.8\pm 5.6, p=0.041$). No significant correlations were found between LF/HF and IR parameters. In MS subjects, the positive correlation of LF/HF with triglycerides could reflect the effects of sympathetic activity on lipolysis. Positive correlations of sympathetic activity with increased lipoprotein levels could rather reflect processes associated with immune system activation/inflammation, than processes involved in glucose homeostasis maintenance.

Key words

Multiple sclerosis • Autonomic nervous system • Autonomic dysfunction • Heart rate variability • Lipoproteins

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Introduction

Multiple sclerosis (MS) is a chronic immune-mediated and inflammatory disease, leading to demyelination and degeneration of the central nervous system (CNS). It mainly affects young adults of working age and is one of the most common causes of invalidity (Thompson *et al.* 2018). Autonomic nervous system (ANS) dysfunction is commonly seen in patients with MS and is characterized by bladder and gastrointestinal disturbances, sexual dysfunction, abnormalities in cardiovascular functions, and sudomotor disorders. Additionally, MS patients report significant fatigue. These symptoms may have a significant impact on patients' quality of life and should be explored as part of the routine examination (Vieira *et al.* 2015, Adamec and Habek 2013, Miglis and Muppidi 2018, Videira *et al.* 2016).

Autonomic dysfunction in MS patients is

assumed to develop due to the impairment of several critical pathways of the autonomic nervous system, including the brain stem, spinal cord, hypothalamus, and cerebral cortex (Gibbons 2019). Demyelinating plaques may disrupt reflex pathways in the insular, cingulate, and ventromedial prefrontal cortices, central nucleus of the amygdala, paraventricular hypothalamus, and the medulla. In addition, the plaques may interfere with the descending autonomic nervous system pathways during their course in the brainstem or spinal cord (Kanjwal *et al.* 2010).

The role of the ANS and mainly the hypothalamus in energetic metabolism is well known (Seoane-Collazo *et al.* 2015). Autonomic dysfunction, especially hyperactivation of the sympathetic branch in combination with poor physical fitness, may be a mechanism associated with early dysregulation of glucose metabolism (Carnethon *et al.* 2003). Recent studies suggest that changes in lipoprotein profile and subclasses are preceded by insulin resistance and hyperinsulinemia in patients with newly diagnosed MS (Radikova *et al.* 2018). Impaired insulin sensitivity may be an underlying cause for catabolism and lipolysis (Anderson *et al.* 1991). The function of ANS can also influence lipolysis and lipoprotein metabolism (Bartness *et al.* 2010). Recent evidence points to an important role of the hypothalamus in triglyceride (TG) metabolism through innervations of liver, white adipose tissue (WAT), and brown adipose tissue (BAT) mainly via sympathetic branches of the ANS. Various neuronal populations, such as neuropeptide Y-expressing neurons and melanocortin-expressing neurons, as well hormones (i.e., GLP-1, leptin, and insulin), modulate sympathetic outflow from the hypothalamus toward target organs and thereby affects peripheral TG metabolism (Geerling *et al.* 2014). Lipolysis caused by increased sympathetic activity could be one of the possible linking mechanisms leading to dyslipidemia in MS. We assumed that increased sympathetic activity in people with MS could be an underlying mechanism involved in catabolism induced by decreased insulin sensitivity and increased lipolysis. Therefore, we analyzed sympathetic/parasympathetic balance in the context of insulin sensitivity and plasma lipid concentrations.

Material and methods

We prospectively enrolled patients from the MS registry of the 1st Department of Neurology, Comenius

University in Bratislava for our study. The inclusion criteria were defined as: patients with newly diagnosed MS after the first episode of symptoms, an EDSS [Expanded Disability Status Scale] score less than 3, age between 18 and 50 years. All patients met the 2010 McDonald's criteria for the diagnosis of MS (Polman *et al.* 2011). Participants with a history of cardiovascular disease, hypertension, diabetes mellitus (type I and II), thyroid disease, current smoking, hepatic or renal disease, malignancy, and acute or chronic infection, or any current medication were excluded from the study. The first MS episode was treated with the pulse, short-term glucocorticoid therapy using methylprednisolone (1000 mg per day intravenously for 3–5 days). The examinations took place before acute treatment or, if not possible, at least 8 weeks after the glucocorticoid therapy. At the time of examination, patients were in remission or without any immunomodulatory therapy. Healthy volunteers served as controls. They were matched with patients for age, sex, and body mass index. All individuals participating in our study signed informed consent. All procedures performed in this study were in accordance with the ethical standards of the National research committee and with the 1964 Helsinki declaration and its later amendments or comparable ethical standards. The study was approved by the Ethics Committee of the University Hospital in Bratislava as well as by the Ethics Committee of Bratislava Self-Governing Region, Bratislava Slovakia (No 110/2016, 00581/2017/HF).

The examination started at 08:00 AM. The subjects were asked to stay fasting for 12 hours and restrain from intense physical activity for 24 hours before the study. Bodyweight and height were measured. Thereafter, the cubital vein was cannulated, and subjects rested for 30 minutes in a comfortable chair to relieve acute stress from venepuncture. They were then placed in a supine position. Subjects remained in this position for 15 minutes. During the whole procedure continuous electrocardiogram and chest respiratory movements were recorded (PowerLab, ADInstruments Pty Ltd, Bella Vista, NSW, Australia). Heart rate variability (HRV) analysis (Chart HRV module, ADInstruments Pty Ltd) was performed on 5 min long parts of recordings. Following HRV parameters were calculated: total power (TP) in the range 0.00–0.40 Hz, low-frequency power (LF) in the range 0.04–0.15 Hz, high-frequency power (HF) in the range 0.15–0.40 Hz, LF/HF ratio, and LF and HF powers in normalized units (LFnu, HFnu).

HF parameter reflects mainly respiratory sinus arrhythmia and is used as an index of cardiac vagal control, LF provides an estimation of cardiac sympathetic activity, LF/HF ratio is used as a marker of cardiac sympathovagal balance (Vlcek *et al.* 2008).

After HRV assessment, subjects underwent a classic oral glucose tolerance test (oGTT). They drank a solution containing 75 g of glucose in 150 ml of water and the blood samples were taken at 0, 15, 30, 45, 60, 90, and 120 minutes. Blood samples were centrifuged at 4 °C and aliquots of sera and plasma were stored frozen at -70 °C until assayed. Insulin sensitivity/resistance indices were calculated using fasting (Matthews *et al.* 1985) and oGTT-derived glucose and insulin concentrations (Cederholm and Wibell 1990, Matsuda and DeFronzo 1999) as used previously in MS patients (Penesova *et al.* 2015).

In fasting conditions, plasma glucose concentrations and fasting serum total cholesterol (TC), low-density lipoprotein (LDL), high-density lipoprotein (HDL), and triglyceride (TG) levels were determined by standard procedure with enzymatic kits (Roche Diagnostics, Lewes, UK) using an autoanalyzer (Siemens Healthcare Diagnostics Inc., Tarrytown, NY, USA). Plasma insulin levels were measured by ELISA kits (ALPCO Diagnostics, Salem, NH, USA). Lipoprotein subfraction analysis was performed using high-resolution polyacrylamide gel electrophoresis technique – Lipoprint system (Quantimetrix Corporation, Redondo Beach, CA, USA), which enabled to analyze the following lipoprotein subfractions profile: the very-low-density lipoprotein (VLDL) fraction, the intermediate-density lipoproteins (IDL) C, B, and A, the low-density lipoprotein (LDL) with subfractions 1 and 2 (large LDL) and subfractions 3 to 7 (small dense LDL – sdLDL), and the high-density lipoprotein (HDL) subfractions categorized into large (subfractions 1–3), intermediate (subfractions 4–7), and small HDL (subfractions 8–10), as previously described (Radikova *et al.* 2018). The hypertriglyceridemic waist phenotype was set. It was defined as a waist circumference of ≥ 85 cm and a triglyceride level of ≥ 1.5 mmol/l in women, and waist circumference of ≥ 90 cm, and a triglyceride level of ≥ 2.0 mmol/l or more in men (Blackburn *et al.* 2008).

The statistical analyses were assessed with SPSS version 18 (SPSS Inc., Chicago, USA). Categorical variables were expressed as numbers (%), continuous variables as means (\pm standard deviation), or median (interquartile range [IQR], minimal-maximal values)

according to the normality of their distribution. The chi-square test, Mann-Whitney U test, and Student t-test were used for group comparisons of variables between MS patients and controls. To determine the relationships between HRV, lipoprotein levels, and IR parameters, Spearman and Pearson correlation coefficients were used. All tests were 2-sided and values of $P < 0.05$ were considered statistically significant.

Results

The study population consisted of 32 MS subjects and 29 healthy controls matched for age, sex, and body mass index. Characteristics of the study groups are included in Table 1. There was no significant difference in HRV parameters and lipoprotein levels between MS patients and controls. In MS patients, compared to controls, significantly lower values of ISI_{Mat} were found (7.3 ± 3.7 vs. 9.8 ± 5.6 , $p = 0.041$). Other parameters of insulin sensitivity and resistance (IR_{HOMA} and ISI_{Ced}) were comparable between groups.

The LF/HF ratio positively correlated with the value of triglycerides ($r = 0.413$, $p = 0.021$) in MS patients, but not in the control group (Table 2). In both groups, we failed to find any significant correlations between LF/HF and parameters of insulin sensitivity or resistance (ISI_{Mat} , IR_{HOMA} , ISI_{Ced}) (Table 3).

Discussion

The results of our study confirm the previous findings of decreased whole-body insulin sensitivity in patients with newly diagnosed MS compared to the controls (Penesova *et al.* 2015). We failed to find any significant differences between the groups in HRV parameters and lipoprotein levels. However, a significant positive correlation was found between LF/HF and triglycerides ($r = 0.413$, $p = 0.021$) in MS subjects, but not in controls. On the other hand, no significant correlations of LF/HF with IR parameters were found.

In our current study, lipoprotein levels and ANS parameters were comparable between MS patients and healthy controls. The role of lipoprotein metabolism and ANS regulation in MS progression seems to be complex and possibly bidirectional. Some studies, in contrast with our study, revealed that MS patients had higher TG, LDL, and lower HDL than control subjects (Fahmi *et al.* 2020, Winstock-Guttman *et al.* 2011, Sicras-Mainar *et al.* 2017). However, when compared to our study with newly

Table 1. Characteristics of the study population

	MS	Control group	P
N	32	29	
Age	30.2 ± 7.1	29.8 ± 6.7	0.809
Women/men	19/13 (59.4/40.6 %)	17/12 (58.6/41.4 %)	0.952
Body mass index (kg/m ²)	23.1 ± 4.2	23.9 ± 4.7	0.479
Waist circumference (cm)	83.1 ± 10.5	83.5 ± 12.5	0.894
TP (ms)	2988.1 (3553.3; 755.4-14521.8)	3232.3 (5857.2; 448.2-14491.9)	0.394
LF (nu) at rest	55.0 ± 18.2	52.4 ± 17.4	0.572
HF (nu) at rest	40.5 ± 17.3	43.4 ± 16.5	0.513
LF/HF at rest	1.4 (1.8; 0.3-5.1)	1.3 (1.1; 0.2-5.4)	0.593
Fasting glucose (mmol/l)	5.0 ± 0.4	4.8 ± 0.4	0.054
Glucose at 120 min. of oGTT (mmol/l)	6.5 ± 1.7	6.0 ± 1.7	0.208
Fasting insuline (mIU/l)	4.5 (2.4; 1.8-24.6)	4.7 (5.4; 1.1-10.1)	0.554
Insulin at 120 min. of oGTT (mIU/l)	42.8 (44.2; 12.8-150.6)	31.9 (24.9; 4.9-92.2)	0.029*
ISI _{Mat}	7.3 ± 3.7	9.8 ± 5.6	0.041*
ISI _{Ced}	55.6 ± 15.7	63.4 ± 17.1	0.068
IR _{HOMA}	1.0 (0.6; 0.4-5.9)	1.0 (1.1; 0.2-2.2)	0.419
Total cholesterol (mmol/l)	4.3 ± 0.8	4.1 ± 0.7	0.253
Hypercholesterolemia (>5 mmol/l)	6 (18.8 %)	2 (6.9 %)	0.171
Triglycerides (mmol/l)	0.8 ± 0.4	0.9 ± 0.6	0.409
Hypertriglyceridemia (>1.7 mmol/l)	1 (3.1 %)	3 (10.3 %)	0.255
Hypertriglyceridemic waist phenotype	2 (6.3 %)	2 (6.9 %)	0.919
LDL cholesterol (mmol/l)	2.6 ± 0.7	2.5 ± 0.6	0.532
LDL 1-2 (mg/dl)	27.0 (37.0; 0-70.0)	34.0 (30.0; 0-69.0)	0.641
LDL 3-7 (mg/dl)	0 (2.0; 0-27.0)	0 (2.0; 0-28.0)	0.906
HDL cholesterol (mmol/l)	1.4 ± 0.3	1.4 ± 0.4	0.751
Large HDL (mg/dl)	21.0 (15.0; 7.0-81.0)	21.0 (20.5; 8.0-45.0)	0.900
Medium HDL (mg/dl)	24.7 ± 5.2	24.1 ± 5.3	0.676
Small HDL (mg/dl)	4.0 (3.0; 0-12.0)	5.0 (4.0; 0-10.0)	0.340
VLDL (mg/dl)	25.8 ± 8.4	25.8 ± 7.1	0.982
IDL (mg/dl)	50.0 ± 19.2	43.7 ± 13.3	0.149

The values in the table are given as number (%), mean ± standard deviation or median, interquartile range, range. TP: total power in normalized units, LF: low frequency power in normalized units, HF: high frequency power in normalized units, IR_{HOMA}: insulin resistance index, ISI_{Mat}: whole body insulin sensitivity index, ISI_{Ced}: peripheral insulin sensitivity index, VLDL: very low-density lipoprotein, IDL: intermediate-density lipoprotein, LDL: low-density lipoprotein, HDL: high-density lipoprotein

diagnosed MS, all of these studies included subjects with longer disease duration (average duration > 4 years) and multiple subjects in these studies received disease-modifying therapy. Autonomic dysfunction is common in MS and it is supposed that sympathetic dysfunction may contribute to the enhancement of inflammatory and neurodegenerative pathways underlying MS progression (Racosta *et al.* 2016). Autonomic dysfunction and a significant increase of sympathetic activity during the early stages of MS have been described previously. However, data from newly diagnosed subjects without any disease-modifying therapy are rare (Racosta *et al.*

2016, Findling *et al.* 2020). In the current study, we found no significant differences in HRV parameters between MS subjects and controls. This finding suggests no significant sympathetic nervous system overactivation or autonomic dysfunction in newly diagnosed MS subjects. This could be explained by only a subtle impairment of critical autonomic nervous system pathways by demyelinating plaques in the early stages of MS. Previously, it was demonstrated that longer MS duration led to progressive impairment of cardiac autonomic balance assessed by HRV (Mahovic *et al.* 2007).

Table 2. Correlations of LF/HF and lipoprotein levels

	MS		Control group	
	r	p	r	P
Total cholesterol	0.328	0.072	-0.189	0.327
Triglycerides	0.413	0.021*	0.034	0.859
LDL	0.233	0.206	-0.189	0.327
LDL1-2	0.214	0.256	-0.028	0.886
LDL3-7	0.158	0.405	-0.115	0.553
HDL	0.063	0.736	0.124	0.520
Large HDL	0.091	0.632	-0.140	0.468
Intermediate HDL	-0.015	0.937	0.066	0.733
Small HDL	-0.010	0.958	0.316	0.095
VLDL	0.286	0.125	-0.095	0.623
IDL	0.029	0.880	-0.066	0.733

VLDL: very low-density lipoprotein, IDL: intermediate-density lipoprotein, LDL: low-density lipoprotein, HDL: high-density lipoprotein

Table 3: Correlations of LF/HF at rest with IR parameters

	MS		Control group	
	r	p	r	p
IR_{HOMA}	0.044	0.816	0.311	0.101
ISI_{Mat}	-0.076	0.684	-0.290	0.127
ISI_{Ced}	-0.208	0.262	-0.221	0.249

IR_{HOMA} : insulin resistance index, ISI_{Mat} : whole body insulin sensitivity index, ISI_{Ced} : peripheral insulin sensitivity index

It is known, that sympathetic nervous system activation is an important mechanism involved in lipolysis (Bartness *et al.* 2014). However, there are spare and conflicting data regarding the aspects of dyslipidemia in the MS population and the role of ANS in this process remains unknown (Radikova *et al.* 2018, Noori *et al.* 2019, Giubilei *et al.* 2002, Zhornitsky *et al.* 2016). Autonomic dysfunction, especially sympathetic activation, could be also a mechanism associated with early dysregulation of glucose metabolism (Carnethon *et al.* 2003).

Results of the current study do not support our initial assumption that decreased insulin sensitivity could lead to increased sympathetic activity and subsequent lipolysis in newly diagnosed MS subjects. Consistently with previous studies, we found significantly reduced insulin sensitivity (determined as the ISI_{Mat} index) in MS subjects (Penesova *et al.* 2015, Ruiz-Agüelles *et al.* 2018). Reduced insulin sensitivity in our newly diagnosed MS patients suggests impaired glucose metabolism already at an early stage of the disease, which can gradually unmask with a longer duration of the disease. In our recent study,

we assumed that insulin resistance could precede changes in the lipid profile in the early stage of MS (Radikova *et al.* 2018). We suppose that impairment of glucose metabolism in newly diagnosed MS, which was observed also in this study, could be too subtle and early to induce catabolism and subsequent lipolysis (Andreson *et al.* 1991). We failed to find any associations of IR parameters with increased sympathetic activity (represented by LF/HF), that belongs to the typical processes involved in glucose homeostasis maintenance (Wehrwein *et al.* 2016).

In the group of MS, in contrast to the control group, we found significant positive correlations between the LF/HF and the levels of triglycerides. This finding could suggest an association of sympathetic activity with higher triglyceride levels in patients with MS, but the study is not designed to prove any causality in this relationship. We speculate that this may be considered as the first sign of changes in lipoprotein subclasses in relation to early changes in sympathetic system activity in newly diagnosed MS patients. It is necessary to admit that only a longer follow-up of the patients could indicate

if changes in ANS and lipoprotein profile become more prominent with time in the MS patients when compared to the controls.

However, our findings could suggest that increased sympathetic activity does not belong to the key mechanisms linking an impaired insulin sensitivity with dyslipidemia in MS subjects. No significant correlations of LF/HF with IR parameters were found. We suppose that positive correlations of sympathetic activity with increased lipoprotein levels could rather reflect processes associated with activation of immune system/inflammation, than processes involved in glucose homeostasis maintenance. Similar associations were described in autoimmune inflammatory diseases including rheumatoid arthritis or systemic lupus erythematosus (Szab *et al.* 2017, Kerekes *et al.* 2014). Future prospective studies could help to elucidate this association.

We have to admit that a small sample size is the main limitation of our study. Longer follow-up of our group is also warranted to elucidate trends in ANS and lipoprotein levels change. On the other hand, the findings of our study were not confounded by any use of disease-modifying treatment, and all subjects were considered as “apparently healthy”. The design of our study limits the reliability of the results. Enrollment of a specific population with newly diagnosed MS does not allow deeper analysis of metabolic changes accompanying MS. To increase the reliability of the current results, future studies should include also subgroup with a longer history of the disease.

Abbreviations

ANS, autonomic nervous system; BAT, brown adipose

tissue (BAT); CNS, central nervous system; EDSS, Expanded Disability Status Scale; HDL, high density lipoprotein; HF, high frequency; HRV, heart rate variability; IDL, intermediate-density lipoprotein; IR, insulin resistance; ISI_{Mat} , whole-body insulin sensitivity index; LDL, low-density lipoprotein; LF, low frequency power; MS, multiple sclerosis; oGTT, oral glucose tolerance test; TC, total cholesterol; TG, triglyceride; VLDL, very low-density lipoprotein; WAT, white adipose tissue

Conflict of Interest

There is no conflict of interest.

Acknowledgements

We express our appreciation to the patients and healthy volunteers who participated in the study. This study was supported by the APVV-15-0228 grant, VEGA 2/0129/20 grant, MZ SR 2018/37-LFUK-11 grant, and by The Framework Programme for Research and Technology Development, Project: Building of Centre of Excellency for Sudden Cerebral Vascular Events, Comenius University Faculty of Medicine in Bratislava (ITMS:26240120023), co-financed by European Regional Development Fund.

Authors' Contributions

AP, BK, RI, PS and PT have participated in study conception and design, MS, ZR, MV, RI, AH, and AP have been responsible for acquisition of data, analysis and interpretation of data, MS, MH, PS and BK have been involved in drafting the paper, AP, MV, IZ, BS, ZD and ZR revised the final draft of manuscript for important intellectual content. All authors read and approved the manuscript.

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