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Alteration in lipid profile in multiple sclerosis patients – a preliminary study

Zmiany w profilu lipidowym u pacjentów ze stwardnieniem rozsianym – badanie wstępne

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Abstract

Aim of the study: The aim of this study was to analyse changes in the lipid profile in the blood of multiple sclerosis patients in relation to disability. Multiple sclerosis is a chronic immune-mediated demyelinating disease of the central nervous system, affecting mostly young adults. The pathogenesis is still unclear. Some studies provide evidence that alteration in the lipid profile in multiple sclerosis is associated with clinical deterioration and disability. It still need to be clarified if these changes are caused by chronic inflammation in multiple sclerosis or they are part of the pathogenetic mechanism. **Materials and methods:** We retrospectively studied the lipoprotein profile (total cholesterol level, LDL, HDL, triglycerides) in 27 patients with the diagnosis of relapsing-remitting multiple sclerosis. The age of the patients ranged between 26 and 60 years. Neurological disability was assessed using the Expanded Disability Status Scale (EDSS). The control group consisted of 12 subjects hospitalised because of a tension-type headache. **Results:** We observed a significantly increased level of total cholesterol, HDL, and a decreased level of triglycerides in multiple sclerosis patients compared to the control group. Moreover, we found a positive correlation between the LDL level and EDSS score of multiple sclerosis patients ($p < 0.05$). We did not observe any correlation between total cholesterol, triglycerides or the HDL level and EDSS score of multiple sclerosis patients. **Conclusion**: An increased lipid concentration in blood is present in multiple sclerosis patients and may correlate with disease activity.

Keywords: multiple sclerosis, lipid profile, cholesterol, LDL, HDL

Streszczenie

Cel pracy: Celem niniejszego badania jest ocena zaburzeń lipidowych u pacjentów ze stwardnieniem rozsianym w korelacji z nasileniem stopnia niepełnosprawności. Stwardnienie rozsiane to przewlekła demielinizacyjna choroba związana z zaburzeniami immunologicznymi, dotykająca głównie młodych dorosłych. Patogeneza choroby jest wciąż nieznana. Niektóre badania wskazują, iż nasilenie zmian w profilu lipidowym u pacjenta ze stwardnieniem rozsianym wiąże się ze stopniem jego niepełnosprawności. Konieczne jest wyjaśnienie, czy zmiany te wynikają z przewlekłego stanu zapalnego występującego w stwardnieniu rozsianym, czy też związane są z mechanizmami patogenetycznymi rozwoju choroby. **Materiał i metodyka:** Retrospektywnie zbadano profil lipidowy (całkowity poziom cholesterolu, LDL, HDL, trójglicerydy) 27 pacjentów z postacią rzutowo-remisyjną stwardnienia rozsianego. Wiek pacjentów poddanych analizie mieścił się w przedziale 26–60 lat. Stopień niepełnosprawności określany był za pomocą rozszerzonej skali niepełnosprawności (Expanded Disability Status Scale, EDSS). Grupę kontrolną stanowiło 12 pacjentów hospitalizowanych z powodu napięciowych bólów głowy. **Wyniki:** Zaobserwowano istotnie zwiększone stężenie cholesterolu całkowitego i HDL oraz obniżone stężenie trójglicerydów u osób ze stwardnieniem rozsianym w porównaniu z grupą kontrolną. Ponadto wykazano pozytywną korelację pomiędzy stężeniem LDL a wartością EDSS ($p < 0,05$). Nie zaobserwowano natomiast korelacji pomiędzy stężeniem cholesterolu całkowitego, trójglicerydów i HDL a EDSS u pacjentów ze stwardnieniem rozsianym. **Wnioski:** Obserwowany wzrost stężenia lipidów w surowicy pacjentów ze stwardnieniem rozsianym może odgrywać rolę w patogenezie choroby i być skorelowany z jej aktywnością.

Słowa kluczowe: stwardnienie rozsiane, profil lipidowy, cholesterol, LDL, HDL

INTRODUCTION

Multiple sclerosis (MS) is a chronic, inflammatory-degenerative disorder of the central nervous system (CNS). Symptoms result from the formation of disseminated, demyelinating lesions both in the brain and the spinal cord. MS affects primarily young adults, causing muscle weakness, difficulties with coordination and speech, and visual problems. The aetiology of MS is not yet well known, but an autoimmune process is considered as the main cause. Autoreactive T-cells migrate through the blood–brain barrier (BBB) (Jatczak-Pawlik et al., 2016), and mediate the autoimmune response against myelin antigens, leading to inflammation and axonal degeneration in the CNS (Bar-Or and Darlington, 2011).

There are a few clinical subtypes of MS. One of them is relapsing-remitting MS (RRMS) characterised by relapses associated with demyelination and followed by complete or partial remission of MS symptoms. Another subtype is secondary progressive MS (SPMS), where after the RRMS phase, the clinical state gradually and continuously deteriorates. Primary progressive MS (PPMS) is characterised by constant progression (Polman et al., 2011).

There are studies suggesting that MS is associated with an altered lipoprotein profile (Fellows et al., 2015; Jorissen et al., 2017; Mandoj et al., 2015; Zhornitsky et al., 2016). The reason for this finding is still unclear. Lipoproteins are essential for the regulation of the inflammatory response and act as are mediators of cholesterol transport (Hansson and Hermansson, 2011).

Low-density lipoprotein (LDL) particles may be oxidised (ox-LDL), which leads to proinflammatory and proatherogenic reactions on the arterial wall (Tabas et al., 2007). Ox-LDL exert the inflammatory response with macrophages, dendritic cells, natural killer T (NKT) cells, and T-cells (Soto et al., 2009). Moreover, LDL oxidation results in the formation of new epitopes which are highly immunogenic and generating autoantibodies (Ferretti and Bacchetti, 2011; Soto et al., 2009). In post-mortem MS brain, in the early and active demyelinating plaques, the existence of ox-LDL was reported (Newcombe et al., 1994). As LDL is synthesised only in the peripheral tissue and cannot penetrate through the intact BBB, it is suggested that damage to the BBB leads to the presence of plasma LDL in MS brain lesions (Carlsson et al., 1991; Ferretti and Bacchetti, 2011; Newcombe et al., 1994). Oxidation of LDL in the early plaques may have a significant role in the demyelinating process (Ferretti and Bacchetti, 2011; Zhornitsky et al., 2016).

High-density lipoprotein (HDL) particles have antioxidant features and they regulate anti-inflammatory cytokine management (Scanu et al., 2008). Several studies show that HDL reduces the harmful effect of ox-LDL, prevents endothelial cell dysfunction and activation, and protects biological membranes (Ferretti and Bacchetti, 2011; Negre-Salvayre et al., 2006; Podrez, 2010; Soto et al., 2009; Zakrzewska-Pniewska et al., 2013). HDL also participates in the transport of cholesterol away from the arterial wall (Navab et al., 2005). Apolipoprotein A-I (ApoA-I), a main protein component of HDL, inhibits macrophage cytokine production induced by T-cells, resulting in decreased inflammatory response in the CNS (Barter et al., 2004; Gardner and Levin, 2015; Jorissen et al., 2017). HDL can be synthesised in the periphery and in the brain, and can partially pass through the BBB (Di Paolo and Kim, 2011). Some studies prove that also HDL may be oxidised (ox-HDL) and acquire proinflammatory features (Navab et al., 2005).

Cholesterol is one of the main components of the myelin sheaths. It is a structural component for cellular membranes, and contributes to synapse and dendrite formation (Goritz et al., 2005; Pfenninger, 2009; Zhang and Liu, 2015). Due to the BBB, cholesterol metabolism and synthesis are separated from the peripheral tissue (Zhang and Liu, 2015). In many neurodegenerative diseases, such as Alzheimer's disease, Huntington's disease and Parkinson's disease, defects in brain cholesterol metabolism has been revealed (Block et al., 2010; Puglielli et al., 2003; Wang et al., 2011). There are many studies showing an alteration in cholesterol levels in MS patients (Zhornitsky et al., 2016). The potential role of abnormalities in cholesterol metabolism in MS patients still need to be studied.

The aim of this study was to analyse changes in lipid profile in the blood of MS patients in relation to the disability score.

MATERIALS AND METHODS

Patient characteristics

This was a retrospective study. In our research, we assessed the lipoprotein profile (total cholesterol level, LDL, HDL, triglycerides – TG) in 27 patients with MS diagnosed according to the McDonald 2010 criteria (Polman et al., 2011). The control group consisted of 12 patients hospitalised because of tension headaches without structural damage to the central nervous system and without any cardiovascular diseases. The age of the patients ranged between 26 and 60 years.

Characteristic	All patients ($N = 23$)	Natalizumab ($n = 7$)	Fingolimod ($n = 13$)	Dimethyl fumarate ($n = 3$)	p-value
Females/males	18/5	6/1	10/3	2/1	0.7869
Age	39.91 ± 7.73	36.86 ± 6.23	40.31 ± 8.57	45.33 ± 4.73	0.1591
Disease duration	8.26 ± 4.56	7.14 ± 3.72	9.15 ± 4.96	7.00 ± 5.29	0.5431
EDSS	2.80 ± 1.46	2.57 ± 1.34	2.73 ± 1.67	3.67 ± 0.29	0.5608

Tab. 1. Demographic and clinical characteristics of treated MS patients. Continuous variables presented as means with standard deviation

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	Multiple sclerosis ($N = 27$)	Control group ($N = 12$)	p-value
Age (years)[B]	39.91 ± 7.73	33.33 ± 10.62	0.0819
Cholesterol [mmol/l] [3–5][A]	5.57 ± 1.23	4.59 ± 0.72	0.0035
LDL [mmol/l] [<1,8][A]	3.35 ± 1.09	2.57 ± 0.54	0.3385
TG [mmol/l] [<1,7][B]	1.24 ± 0.64	1.48 ± 0.83	0.0049
HDL [mmol/l] [>1,2][A]	1.69 ± 0.41	1.35 ± 0.40	0.0221

[A] Calculated with Welch's *t*-test.
[B] Calculated with Mann–Whitney *U*-test.

Tab. 2. Comparison between the patients with MS and the control group

The clinical characteristics of the MS group are presented in Tab. 1.

All patients were diagnosed with RRMS. They did not have any concomitant diseases. Neurological disability was assessed using the Expanded Disability Status Scale (EDSS). Patients in the MS group were treated with disease-modifying therapies (DMTs) including natalizumab, fingolimod, and dimethyl fumarate. Twelve age- and sex-matched control subjects were recruited from patients with tension-type headache. The patients were free from any structural brain damage based on magnetic resonance imaging (MRI).

The exclusion criteria for all subjects included the history of cardiovascular diseases, previous statin treatment, diabetes mellitus, severe liver disease, autoimmune diseases, cancers, and other systematic or chronic diseases.

All patients were hospitalised in the Department of Neurology and Stroke, Medical University of Lodz, Poland, between 2018 and 2020.

Methods

Total cholesterol, LDL, HDL and TG level measurements were performed in a fasting state in all the study patients. Total cholesterol and HDL levels were determined enzymatically with Olympus AU 6400 analyser. LDL levels were estimated by the Friedewald formula.

MRI evaluation and cerebrospinal fluid analyses were performed in all MS patients to confirm the diagnosis. The antinuclear antibodies (ANA) and antineutrophil cytoplasmic antibodies (ANCA) were negative, and vitamin B_{12} levels in the blood were at a normal level in all MS patients. The studies were performed in the course of the diagnostic process during the patients' previous hospitalisations.

	Correlation coefficient	p-value
Cholesterol [mmol/l] [3–5][A]	0.3716	0.067
LDL [mmol/l] [<1.8][A]	0.4086	0.043
TG [mmol/l] [<1.7][B]	0.0129	0.951
HDL [mmol/l] [>1.2][A]	0.0210	0.921

[A] Calculated with Pearson's correlation coefficient.
[B] Calculated with Spearman's correlation coefficient.

Tab. 3. Correlation coefficients between the lipid profile and EDSS

Statistical analysis

Descriptive statistics were used to summarise the clinical and demographic features of MS patients. The resulting data are presented as means with standard deviations. The distribution of variables was calculated with the Shapiro–Wilk test. Due to non-parametrical distribution, the differences between the groups were estimated using the Mann–Whitney *U* test. To evaluate the differences between >2 groups, Kruskal–Wallis ANOVA was used. Correlations between variables were calculated with Spearman's correlation coefficients. A p-value <0.05 was considered significant. All analyses were done with the GraphPad Prism 6 software.

RESULTS

In our study, we observed important changes in the lipoprotein profile of RRMS patients. The total cholesterol ($p < 0.005$) and HDL ($p < 0.05$) levels were substantially increased in MS patients compared to the control group. Moreover, we noticed a significantly decreased level of TG ($p < 0.005$) in the study group (Tab. 2, Fig. 1). Another interesting finding of our study is a positive correlation found between the LDL level and EDSS score of MS patients ($p < 0.05$) (Tab. 3, Fig. 2).

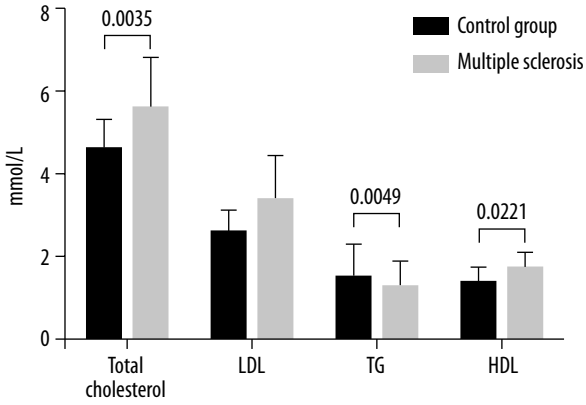

Fig. 1. Comparison of the lipid profile among the control and study groups with significant pvalues. Mean values presented as boxes, standard deviation presented as whiskers

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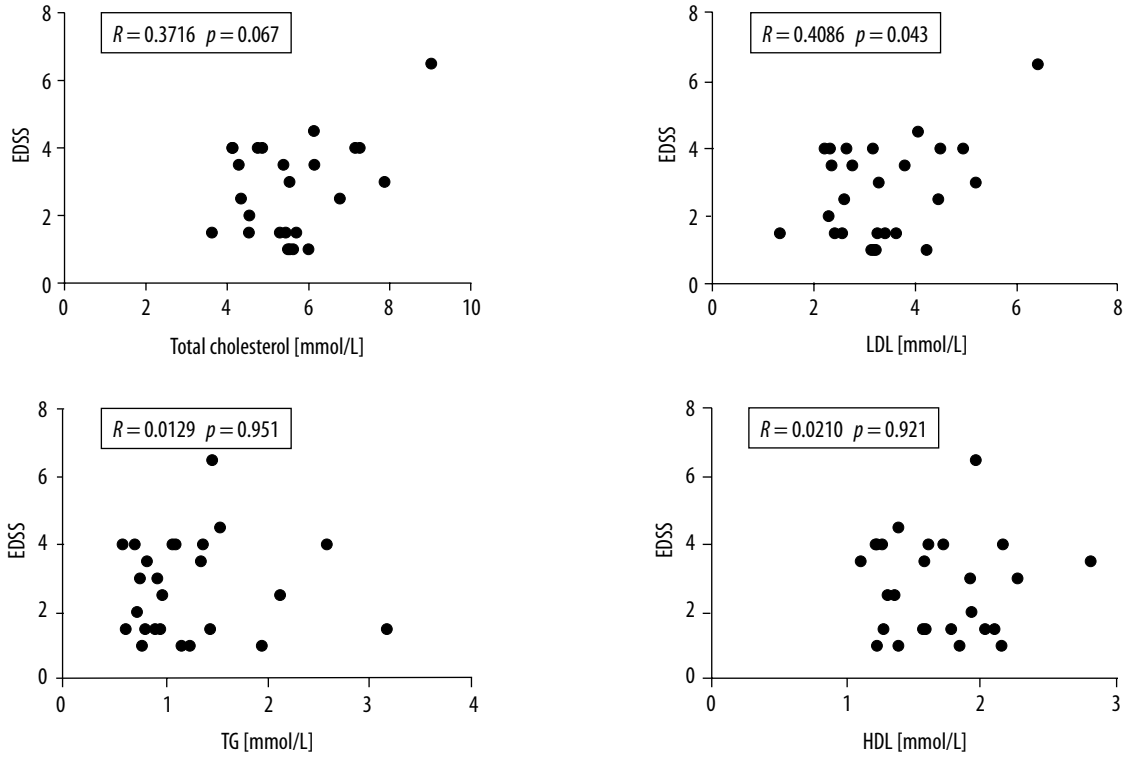

Fig. 2. Correlation plots between the lipid profile and EDSS. Correlation coefficients with exact p*-values are indicated in each case*

DISCUSSION

The effect of lipid disturbances on the pathogenesis of MS is unclear, however, many studies suggest that MS is associated with an altered lipoprotein profile (Fellows et al., 2015; Jorissen et al., 2017; Mandoj et al., 2015; Zhornitsky et al., 2016).

In our research, we observed a significant increase in the total cholesterol level in MS patients compared to the control subjects, and we also noticed a positive correlation between the LDL level and EDSS score in our patients. We had expected to find a correlation between the total cholesterol level and clinical disability in MS, but it was not found, which may be due to the small study groups. Our data are consistent with the previous studies which found that elevated circulating LDL and/or total cholesterol levels were associated with adverse outcomes in MS (Browne et al., 2014; Mandoj et al., 2015; Palavra et al., 2013; Weinstock-Guttman et al., 2011) and indicated an important role of cholesterol in neuronal physiology. The observation may suggest that LDL metabolism may have a negative impact on the progression of disability in MS.

Previous studies support the theory that the important role of lipids in MS pathogenesis and progression is related to oxidative stress in the brain (Gonsette, 2008; Jorissen et al., 2017). The process of accumulation and oxidation of LDL in the arterial wall is associated with chronic inflammation, which is a part of the pathogenesis of both atherosclerosis and MS (Hansson and Hermansson, 2011). Ox-LDL is a product of peroxidation of LDL. This mechanism produces highly reactive aldehyde particles. During this process, the conversion of apolipoprotein B (ApoB) takes place. Converted ApoB is recognised by macrophages, which leads to the absorption of ox-LDL and the creation of foam cells. The process creates plaques in arterial walls (Tabas et al., 2007). Interestingly, some studies provide evidence that the particles which are part of the oxidative process in atherosclerosis pathogenesis were also found in the early and active demyelinating plaques in MS (Newcombe et al., 1994). This may explain the positive correlation between the LDL level and the elevated EDSS score or clinical deterioration in MS patients. Other studies suggest that ox-LDL is a better predictor of elevated EDSS than LDL (Palavra et al., 2013; Tettey et al., 2014). Esterified cholesterol was also found in MS demyelinating plaques (Newcombe et al., 1994). The finding suggests that those cholesterol esters originate from CNS myelin and circulating LDL. As mentioned before, LDL is synthesised only in the peripheral tissue and cannot penetrate through the intact BBB. The leakage of LDL is possible after BBB damage. It has been proven in animal studies that elevated circulating cholesterol levels can increase the permeability of the BBB (Jiang et al., 2012). This points towards the role of cholesterol in MS pathogenesis or progression of the disease. Chronic hypercholesterolaemia can enhance immune response, promoting inflammation at the vascular endothelium and resulting in the dysregulation of cell adhesion. The process causes endothelial dysfunction and contributes

to the extravasation of immune cells to the CNS (Sitia et al., 2010). Hypercholesterolaemia can induce an increase of the circulating LDL level and BBB dysfunction. These changes indirectly lead to the oxidation of LDL and intensification of the immune response, which contributes to neurotoxic effects (Zhornitsky et al., 2016).

Our research also showed significantly elevated HDL levels in MS patients compared to the healthy group. Published studies show divergent results in terms of the alteration of HDL levels in MS patients. Some of them showed a decrease (Meyers et al., 2014), others found an increase (Giubilei et al., 2002; Jorissen et al., 2017) in the HDL level. The discrepancy may result from the lack of distinction between specific subclasses of HDL (small, intermediate, large). Ox-HDL was not measured in those studies. Generally, an increased level of HDL is associated with a protective function by counteracting the negative proinflammatory effects of ox-LDL and other mediators of inflammation and oxidative stress (Barter et al., 2004; Navab et al., 2005). One of the main tasks of HDL is the maintenance of cholesterol homeostasis and cholesterol efflux from the arterial wall (Jorissen et al., 2017; Murphy et al., 2008). We observed that in our study total cholesterol and HDL levels were elevated simultaneously. The finding was also presented in many other studies (Jorissen et al., 2017; Mandoj et al., 2015; Tettey et al., 2014; Zhornitsky et al., 2016). This may suggest that HDL anti-inflammatory and cholesterol transport functions are impaired in MS. Other studies emphasise the role of HDL oxidation (Ferretti and Bacchetti, 2011; Jorissen et al., 2017). Moreover, some *in vitro* studies indicate that ox-HDL and ox-LDL have a toxic impact on microglia and astrocytes, and can lead to oxidative stress and neuronal degeneration (Keller et al., 1999; Kivatinitz et al., 1997).

Chronic inflammatory diseases may induce HDL oxidation, which can promote proinflammatory and pro-oxidant responses (Navab et al., 2005). Furthermore, several studies provide evidence for elevated levels of biochemical markers of lipid peroxidation in the blood of MS patients (Bizzozero et al., 2005; Ferretti et al., 2005; Haider et al., 2011; Miller et al., 2011). That might result from BBB dysfunction or can be caused by peripheral immune cell activation by the chronic inflammation process. The neurotoxic effect of lipid peroxidation can contribute to axonal injury and demyelination in MS.

CONCLUSION

Extensive evidence supports the association between abnormal lipoprotein metabolism and MS inflammatory responses and the pathogenesis of neurodegeneration. An alteration in the lipid profile may lead to a better understanding of MS pathogenesis and be useful as a potential marker of disease progression. We realise that the main limitation of our study is the small number of patients in the study groups, but this work is a preliminary one. We are going to continue this line of research, and we believe that the significant statistical differences found so far are worth publishing.

Conflict of interest

The authors do not declare any financial or personal links to other persons or organisations that could adversely affect the content of this publication or claim rights thereto.

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