The Value of Neurospecific Protein S-100 and Lipoproteins in the Development of Multiple Sclerosis

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Abstract

This article describes the clinical picture of multiple sclerosis (MS) depending on indices of the neurospecific protein s-100β and low-density lipoproteins. In patients with MS in the phase of activity, high levels of s-100β protein and LDL were found. It means that in patients with MS, demyelination and degeneration process continues, and as a result, patients are more likely to develop new symptoms. Thus, the study results of s-100β protein and LDL can be used to predict possible development of adverse symptoms in multiple sclerosis.

Keywords: *Multiple sclerosisneurospecific protein lipoproteins central nervous systemdemyelinating diseases.*

Introduction

Multiple sclerosis (MS) is a fairly widespread dysimmune neurodegenerative disease of the central nervous system, affecting mainly young people and almost inevitably causes disability at a certain stage of its development. Early diagnosis of multiple sclerosis is considered one of the most significant tasks of modern neurology. The etiology, pathogenesis and factors, affecting demyelination in multiple sclerosis, are still not clearly understood.

Demyelinating diseases belong to the group of autoimmune diseases, develop with destruction of the myelin sheaths in the central and peripheral nervous system. According to scientific literature, this process is caused by imbalance of 1,2,3-group cytokines of T-lymphocytes. An increase in the activity of T-1 lymphocytes leads to an increase in pro-inflammatory cytokines: IL-2, TNF-alpha, IFN-gamma, IL-12, causing a loss of tolerance to autopeptides and enhancement of autoimmune processes[5]. Synthesized “anti-myelinic” “antibodies” leading to central nervous system demyelination, dramatically reduce impulse conduction along nerve fibres. In patients’ blood, in relation to antigens of brain structural elements, that is, oligodendrocytes - to myelin basic protein (MBP), S-100 glial protein, antibodies are formed and detected[3]. The detected S-100 glial protein is considered to be an inducer of glial cell destruction. Sensitivity to this immunocyte protein in 70% of cases is determined in the blood; it is explained by destruction of glia and neurons. Also, in 50% of cases, the integrity of neuronal membranes is broken. The following types of s-100 protein are present: s-100 άά (specific to skeletal muscles, heart muscles, kidneys, liver); s-100 άβ (specific to glial cells, melanocytes); s-100 ββ (specific to Schwann cells). An increase in the concentration of s-100 άβ and s-100 ββ in cerebrospinal fluid and plasma is a brain damage marker. The results of s-100 study can be used to predict possible development of adverse symptoms in multiple sclerosis. In humans, elevated S100B levels have been detected in various clinical conditions. Brain injury and ischemia are associated with an increase in S100B concentration, probably, due to destruction of astrocytes. In neurodegenerative, inflammatory and mental diseases, elevated S100B levels may be caused by secreted S100Bs or release from damaged astrocytes. This review summarizes published S100B data regarding human brain damage and neurodegeneration[6]

An increase in the level of this protein is detected in the cerebrospinal fluid and blood plasma of patients with MS with exacerbation[4].

In MS pathogenesis, lipid storage disease is also

present. Lipids comprise 70% of the myelin sheath dry weight. They are structurally and functionally significant, their composition under demyelinating diseases undergoes great changes. The lipids involvement in all 4 development stages of the demyelinating process is demonstrated. In animal models, encephalithogenicity of myelin glycolipids was shown[7]. Thus, lipids may act as ligands of innate immunity receptors or pro-inflammatory agents that potentiate activity of innate immunity receptors and affect the inflammatory process with demyelinating diseases.

Despite great successes in documenting cellular and molecular mechanisms, underlying multiple sclerosis pathophysiology, the autoimmunity structure also cannot provide an exhaustive explanation of the disease etiology. I propose a new framework for MS as a lipid metabolism dysfunction. In particular, lipid metabolism homeostasis is destructed during the acute phase of inflammatory response, induced by a pathogen, trauma or stress, starting a feedback loop of increased oxidative stress, inflammatory response and proliferation of cytotoxic foam cells, crossing the blood-brain barrier, catalysing myelin and preventing remyelination. Understanding MS as a chronic metabolic disorder, makes it possible to single out four aspects of the disease onset and progression: 1) its pathophysiology; 2) genetic susceptibility; 3) environmental and pathogenic triggers; and 4) asymmetric sex ratio in patients. It also provides new treatment options.[2].

Cholesterol is an important component of mammalian cell and myelin membranes. In this systematic review we studied the relationship between cholesterol levels and cholesterol turnover markers in blood circulation and/or cerebrospinal fluid (CSF) and disease outcomes in adults with clinically isolated syndrome (CIS) or confirmed MS. Studies show that elevated levels of circulating cholesterol of low density lipoproteins (LDL), total cholesterol, and,in particular, apolipoprotein B and oxidized LDL, are associated with adverse clinical and MRI outcomes in MS. These relationships were observed back in the CIS. Studies also show that oxysterols, cholesterol precursors and apolipoprotein E may be a marker of specific disease processes in MS, but further research is required to clarify these processes and relationships. When analysed together, these data mean that cholesterol and cholesterol turnover markers are potentially suitable for clinical use as biomarkers of disease activity and may even be involved in MS pathogenesis. [1]

Purpose of our Study: to study the role and importance of neurospecific protein s-100β and lipid profile indices in the pathogenesis of multiple sclerosis development.

Material and Research Method

40 patients with multiple sclerosis (MS), aged from 21 to 45 years (mean age 33±1.5) were examined. Of these, 14 (35%) were men and 26 (65%) were women. All patients underwent clinical and neurological examinations and head MRI. Patients were divided according to MS course: with remitting MS - 18 (45%), primary progressive MS - 7 (10%) and secondary progressive MS - (15) 37.5%. The study of MS duration from the disease onset showed that patients with duration of "1-5 years" were 58%, "5-10 years" - 22%, "over 10 years" - 20%. There were 26 patients with MS in the active phase (65%), and 14 (35%) in the remission phase. A neurospecific s-100β protein (s-100β protein) (normal < 0.11 μg/L) and low-density lipoproteins (LDL) (normal < 2.5 mmol/L) were studied in blood plasma.

Study Results

The study results showed that in patients with MS, s-100β protein values vary from 0.06 to 0.22 μg/L (mean 0.17±0.09 μg/L). In 70% of cases, this index is higher than normal (28 patients). A study of neurospecific protein indices depending on the disease course showed, that in patients with a remitting course, s-100β protein was 0.14±0.1 μg/L, and, accordingly, in a primary progressive course - 0.21±0.0 μg/L, secondary progressive course - 0.18±0.06 μg/L, that is, in all types of course, s-100β index is increased, but the highest index is registered in the primary progressive course. In MS active phase, s-100β protein index was increased 0.13±0.01 μg/L, and during remission, within the normal range, - 0.08±0.2 μg/L.

The s-100β protein index did not differ by sex. Thus, in men it was 0.12±0.01 μg/L and in women - 0.14±0.02 μg/L.

It was determined that the longer the disease lasts, the more s-100β protein index is increased, regardless of the activity phase. With duration of the disease for "1-5 years" s-100β was 0.16±0.1 μg/L, "5-10 years" - 0.21±0.05 μg/L and "more than 10 years" - 0.2±0.1 μg/L.

Studies showed that in patients with MS, LDL levels ranged from 2.2 mmol/L to 4.65 mmol/L, mean of 3.6±0.1 mmol/L.

In all MS forms, mean LDL value is increased, especially with a secondary progressive course (3.6±0.1 mmol/L), remitting course (3.4±0 mmol/L) and primary progressive course (3.1±0.02 mmol/L).LDL in the active phase (3.5±1.3 mmol/L) differs sharply from that during remission phase (3.0±1.1 mmol/L). There were no gender differences in LDL indices (male - 3.4±0.03 mmol/L and female - 3.4±0.15 mmol/L).

The longer MS duration is, the higher LDL index is. So, with duration of "1-5 years", this index was 3.4±0.01 mmol/L, "5-10 years" - 3.6±0.1 mmol/L, "more than 10 years" - 3.7±0.2 mmol/L.

When protein indices s-100β and LDL were compared, it showed a negative correlation (r = - 0.12).

Conclusions

Evaluation of study results showed, that in all MS forms, the mean index of neurospecific protein s-100β and LDL was increased. It means, that our patients have a demyelinating and neurodegenerative process. A study of the disease duration showed, that the longer the disease lasts, the more intensive demyelination (degeneration) process is. A comparative study, depending on the disease course showed, that in a primary progressive course, the protein index s-100β is permanently high, LDL index is high in a secondary progressive course. Both analysed parameters are higher in the active than in the remission phase. Based on study results, in MS patients, high s-100β protein and LDL indices demonstrate, that in patients with MS the demyelination (degeneration) process continues; as a result, patients are more likely to develop new symptoms.Based on the analysis of studied parameters, depending on MS activation and remission, it can be observed that s-100β protein index in the active phase is increased, whereas in the remission phase it is within the normal range; LDL index is increased in all phases. Logically, patients in active phase of the disease re treated for demyelination (degeneration) processes (hormone therapy, interferons, immune adjuvants). As a result, s-100β protein index in the remission phase is within normal range. However, as a rule, patients with MS do not receive lipid-improving drugs. On the other hand, it takes a long time, on average, 3-6 months to normalize the lipid profile. But, by this time, either the disease exacerbation or the disease progression occurs.

Thus, in MS treatment, the disease phase shall be transferred from the active to remission phase, patients shall also be treated against risk factors, contributing to emergence of demyelination (degeneration) processes. This is a very important tactic for secondary prevention of the disease.

Thus, the study results of s-100β protein and LDL can be used to predict possible development of adverse symptoms in multiple sclerosis.

Ethical Clearance: No ethical approval is needed.

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Conflict of Interest: Nil

References

1. Zhornitsky S. MKA, MLM, TSE, RM. Cholesterol and markers of cholesterol turnover in multiple sclerosis: relationship with disease outcomes. Mult. Scler. Relat. Disord. 2016; 5: p. 53-65.
2. A.P. C. Multiple sclerosis is not a disease of the immune system. Q. Rev. Biol. 2011; 86: p. 287-321.
3. Mitosek-Szewczyk K GKWFDSZ. Some markers of neuronal damage in cerebrospinal fluid of multiple sclerosis patients in relapse. Folia Neuropathol. 2011; 49(3): p. 191-196.
4. Nicoletti F. et al WH, KSJ. 2006, 2012.
5. Rothermundt M PMPJA. V. Microsc Res Tech. 2003 Apr 15; 60(6): p. 614-32.
6. Zhornitsky S. MKA, MLM, TSE, RM. Cholesterol and markers of cholesterol turnover in multiple sclerosis: relationship with disease outcomes. Mult. Scler. Relat. Disord. 2016; 5: p. 53-65.