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Cholesterol Homeostasis and the Pathogenesis of Multiple System Atrophy

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Abstract

Multiple system atrophy (MSA) is a sporadic neurodegenerative disease among adults, which can be characterized by autonomic nerve dysfunction, Parkinsonism, ataxia and pyramidal tract dysfunction, or overlapped symptoms. It can mainly be divided into two types: Parkinsonism (MSA-P) and cerebellum type (MSA-C). The pathology of this disease is the accumulation of alpha-synuclein in oligodendrocyte. And because of this, it belongs to synucleinopathies. Alpha-synuclein is a kind of protein, which has a close connection with lipid membrane in the process of biosynthesis of central nervous system, and this close relationship may play a crucial role in the mechanism of alpha-synucleinopathies. Recently researchers who have focused on the serum lipids level in MSA patients are taking a stab at finding the diagnostic biomarkers, like serum cholesterol level, so as to develop effective therapies in the early stage of MSA. Therefore, the purpose of our review is to summarize the valuable part of recent researches on cholesterol level of MSA patients and to discuss the optimal way to evaluate MSA disease in a simple way to diagnose it early.

Keywords: Multiple system atrophy; Alpha-synuclein

Introduction

Multiple system atrophy [1] is a rapid progressive neurodegenerative disease, clinically among adults, which is characterized by autonomic failure with various combinations of Parkinsonism, cerebellar ataxia, and pyramidal dysfunction. Beyond the current consensus diagnostic criteria proposed by Gilman, MSA patients showed widespread cortical, subcortical, and white-matter alterations in recent researches. Pathololgically, studies had showed that alpha-synuclein accumulation results in MSA and other synucleinopathies like PD, dementia with Lewy bodies (DLB). Nevertheless, in MSA, alpha-synuclein preferentially accumulates in oligodendrocytes [2]. But whether this occurs in a cell-autonomous manner or results from neuronal release, subsequent oligodendrocyte uptake remains mysterious. A research has showed that it is interesting that brain extracts from patients with MSA but not those with PD accelerated the process of neurodegeneration when those brains were injected into transgenic mice. The result of this research suggested that MSA-derived strains of alpha-synulein might be more toxic [3]. Furthermore, brain extracts from different patients with MSA showed variable rates of alpha-synuclein transmission [4]. Importantly, alpha-synuclein strain differences among patients may contribute to patient variability such as age of onset and rate of disease progression. And researches indicated that prognosis of MSA is poor [5].The mean survival after diagnosis is only 3-4 years [6]. In sum, it is this kind of poor symptoms and prognosis of MSA patients push us to investigate more avenues to diagnose it early.

In term of aggregated toxic alpha-synuclein, selective vulnerability of oligodendrocytes in MSA might be mediated by the accumulation and binding of p25, an oligodendrocyte-specific protein [7], or by decreasing glial-derived neurotrophic factor (GDNF) levels [8]. Alpha-synuclein is highly soluble and enriched at presynaptic terminals, where it binds lipids and regulates the release of synaptic vesicles [9,10], Therefore, the important role of serum lipids in MSA diseases is increasingly acknowledged in the clinical scenarios. However, only few reports have examined the role of serum lipids in patients with MSA until now. Here, we sought to review and summarize published studies that investigated the association between serum cholesterol level and the pathogenesis of MSA.

Serum Cholesterol Level of MSA Patients

Current researches on serum lipid level in patients with MSA is relatively limited, only a total of 4 reports in all [11-14]. The earliest one was the study of South Korea in 2009 [11], which firstly showed that in the serum lipid level of patients with MSA, TC, LDL-C, HDL-C levels decreased significantly compared with the control group. Then another research in Chinese people also suggested low level of cholesterol may have connection with the pathogenesis of MSA [12]. Subsequently, another two Chinese studies [13,14] supported their results. Compared with healthy controls, TC, HDL-C, LDL-C level were decreased significantly [11]. In contrast to the previous two studies, they also found that ApoA and ApoB significantly decreased in MSA group [12]. Two of the three Chinese studies [12,14] considered that the results showed the serum lipid levels have no correlation with disease duration in the early stages of the disease and with the entire progress of disease, and stressed that low level of cholesterol maybe an indicator in MSA patients in the early stage of disease (Table 1).

From above four studies, we could conclude that serum cholesterol level of MSA decreased significantly, while the triglyceride level did not. So it could be considered that the imbalance of cholesterol homeostasis was related to the pathogenesis of MSA rather than that of triglyceride. And apolipoproteins is a component of the outer layer of lipoprotein particles, which is the main component for maintaining the structure and function of lipid transportation. Among those apolipoproteins, ApoA is the main HDL protein, and most of the distribution of Apo B is in low density lipoprotein (LDL). That is Apo A and Apo B can directly

Country	Author	No. of cases (Probable MSA/Control)	Published date (Year)	Low level of serum lipids
South Korea [11]	Lee et al.	142/155	2009	TC, HDL
China [12]	Cao et al.	234/240	2014	TC, LDL-C, HDL-C and TG
China [13]	Yanan et al.	113/132	2015	TC,LDL-C, ApoA1 and ApoB
China [14]	Chongfeng et al.	62/63	2015	TC, HDL-C, LDL-C, ApoA and ApoB

Table 1: Four reports focused on the serum lipid level of MSA.

reflect the content of HDL and LDL [15].Thus the role ApoA and ApoB played in transporting cholesterol is crucial and we cannot ignore them in our future research. In two studies [13,14], they found a decrease in apolipoprotein levels in patients with MSA, which reflects the imbalance of cholesterol homeostasis from another angle. Now there is a Japan research, which demonstrated that patients with advanced stage of MSA may develop malnutrition in the absence of a decrease in BMI. Moreover, serum albumin level may be useful for evaluating nutritional changes in MSA patients. Also, they explained that equivalence between caloric intake and caloric expenditure might account for unchanged BMI in these patients. Besides, they suggested that serum lipid levels may serve as a useful indicator of nutritional changes in MSA patients [16]. Another French study [17] focused on risk factors of MSA disease, which showed that MSA was not associated to exposure to pesticides, solvents, and other toxics, and not to occupations, except plant and machine operators and assemblers where the risk of MSA increased with number of years. This case-control study provided new findings on risk factors of MSA, including less education, less fish, sea food and tea, and more alcohol. Regretfully, only limited reports have focused on the nutrition intake and risk factors in patients with MSA. Future studies are necessary to determine the effects of nutritional treatment on patient survival. And more studies still should be required to confirm that low level cholesterol does accompany with MSA patients and is meaningful to instruct clinical diagnosis and efficient treatment.

From recent researches, we can come to a conclusion that extracerebral cholesterol homeostasis has changed in the progression of MSA. Put it another way, cholesterol homeostasis might play a considerable role in the process of MSA disease, or indicate the pathogenesis of MSA. Whether this peripheral variation indicated that intracerebral homeostasis varies accordingly is a tough issue nowadays. Next, we are going to investigate more details on the microcirculation of intracerebral and extracerebral cholesterol homeostasis physiologically and pathologically of MSA.

The Role and Synthesis of Intracerebral Cholesterol

First, the most component of myelin formed by astrocytes is lipid and protein. The lipid content of it is high, up to 70%, other 30% constitute is protein. Although there are no authentic myelin-specific marker lipids until now, myelin invariably contains cholesterol, phospholipids and glycosphingo lipids. The concentration of cholesterol in the brain, and particularly in myelin, is consistent with an essential function related to its membrane properties [18]. Thus, lipid variation maybe an early alteration of myelin sheath damage. In conclusion, in the early phase of MSA disease, lipid variation occurs in myelin sheath and then decrease of lipid level may be an early clue for the onset of MSA, which may play an important role in predicting the risk of MSA [14]. Undoubtedly, the brain is the most cholesterol-rich organ in the body, for the reason that up to 50% of the white matter may be composed of myelin. Overall, the current data provide tantalizing indications that modulation of intracerebral cholesterol levels may be a possible strategy for protecting against MSA.

As we all known, MSA is a degenerative disease of the central nervous system. Thus, we need to figure out the synthesis of intracerebral cholesterol. The source of cholesterol in the human body is complex in our body. Simply put, one is self-synthesis (70-80%), and the other is food intake (20%-30%) [14]. In the developing CNS, Cholesterol self-synthesis is relatively high, it declines to a very low level in the adult stage. And brain cholesterol has a very long half-life, and the half-life of cholesterol has been estimated to be at least 5 years [19]. It was recently pointed out that the long half-life of cholesterol in the brain is remarkable in light of the high metabolic rate of this organ [20]. Assumption has been made that there are interactions between astrocytes and neurons in cholesterol homeostasis according to Pfrieger [21]. Neurons are capable of synthesizing cholesterol, and it has been suggested that in the adult state, neurons rely on delivery of cholesterol from nearby cells such as astrocytes. These exogenous resources might allow the neurons to concentrate on generation of electrical activity and dispense with energetically costly cholesterol synthesis. That Cholesterol delivered to neurons in this way may support synaptogenes is and may be incorporated into synaptic vesicles, a mechanism that may involve activation of the cholesterol transporter ABCA1 [18,22].

Peripheral Cholesterol Reflect Intracerebral Cholesterol of MSA?

It is evident that more energy and nutrients were needed to support intracerebral cholesterol from peripheral cholesterol. But, another tough question we have to give our priority is that how peripheral cholesterol variations mirror intracerebral cholesterol level because of the existence of BBB.

In the past decade, evidence of a possible link between cholesterol and neurodegeneration has been accumulated. As the BBB efficiently prevents the passage of peripheral cholesterol into the brain, the mechanism behind this accumulation remains obscure. The possibility has to be considered that the effect of cholesterol is mediated by effects at the level of the cerebral microcirculation rather than at the level of glial cells or neurons [23]. But, there has been a significant increase of knowledge about cholesterol homeostasis in the brain, and powerful novel experimental tools have been introduced in this field. Until now, there are two kinds of cholesterol markers for MSA patients, 24S-hydroxycholesterol and 27-hydroxycholesterol. Enzymatic conversion of cholesterol into the metabolite 24S-hydroxycholesterol, which is able to cross the blood-brain barrier (BBB), has recently been demonstrated to be the most important excretion mechanism until now [18].

Some studies indicated that there is a correlation between serum levels of 24S-hydroxycholesterol and body surface, and this relationship should always be taken into account when using 24S-hydroxycholesterol as a new biomarker for brain cholesterol homeostasis, which have been proved that it can cross through BBB. Besides, 24S-Hydroxycholesterol is an inhibitor of cholesterol synthesis [20]. In some neurodegenerative disorders such as Multiple Sclerosis, Alzheimer and Huntington disease, plasma 24S-hydroxycholesterol was found reduced proportionally to the degree of brain atrophy as measured by MRI [24].

While our attention should be paid on the serum level of these two cholesterol in our body, Cholesterol 24-hydroxylase (CYP46A1), the enzyme responsible for formation of 24S-hydroxycholesterol, is almost exclusively located in the brain [25]. On the other hand, cholesterol 27-hydroxylase (CYP27A1), the enzyme responsible for formation of 27-hydroxycholesterol, is present in most organs and tissues. Although there is some expression of CYP27A1 in the brain, the levels of the enzymatic product, 27-hydroxycholesterol, in brain tissues are low respectively, only a small part of those of 24S-hydroxycholesterol [26].

Otherwise, the levels of 24S-hydroxycholesterol in the circulation may also be dependent to some extent on the transporting capacity of the lipoproteins in the circulation and/or factors of importance for the activity of the 24S-hydroxylase in the brain. The clearance will also directly affect the plasma levels of this oxysterol. Another oxysterol in the circulation, 27-hydroxycholesterol, originates mainly from extracerebral and extrahepatic sources of cholesterol [26,27]. In a recent study, we found that 24S-hydroxycholesterol and 27-hydroxycholesterol have similar distribution in circulating lipoproteins [28]. In view of this, it is possible that the ratio between 24S-hydroxycholesterol and 27-hydroxycholesterol in the circulation may be a better marker for cholesterol in the brain than the absolute levels of 24S-hydroxycholesterol or 27-hydroxycholesterol.

Other Possible Correlations of Pathogenesis of MSA

In addition to the variation of cholesterol homeostasis ,other researches on the pathogenesis of MSA and the risk factors of MSA is also related to coenzyme Q10 (coenzyme Q10), COQ2 (coenzyme Q2), ABCA family (ATP-binding cassette A), especially ABCA1 and ABCA8. Lipid transporter ABC transporter family is huge, including 48 transporters. It can be further divided into 8 subtypes from A-G, in which ABCA is mainly responsible for the brain and peripheral tissues and cell membrane lipid regulation, including a total of 12 members. A large number of studies show that ABCA subfamily can control the disorder of lipid metabolism and brain, and regulate many nervous systems degenerative disease process [29]. It is possible that one or more members of the ABC transporter superfamily may be involved in the exclusion of circulating cholesterol from the brain. As is mentioned above, transporter ABCA1 is a activator of cholesterol synthesis. It was recently demonstrated that primary porcine brain capillary endothelial cells express mRNA and protein of the cholesterol transporter ABCA1 [30]. It was also shown that along with ABCA1 expression, the oxysterol 24S-hydroxycholesterol enhancedapoA1-dependent efflux of cholesterol from cultured brain endothelial cells. Based on results of experiments with an in vitro model system, the possibility was discussed that the ABCA1 transporter and the scavenger receptor SR-B1 may be involved in an autoregulatory mechanism for backward of cholesterol to the brain. While, Turunen et al. [31] have showed that ABCA8 is highly expressed in oligodendrocytes that is less abundant in the white matter in the brain. ABCA8 stimulates oligodendrocytes to produce sphingomyelin and is presumably likely to maintain and play an important role in the formation of myelin. So it is a potential valuable study of this disease. Vitro experiments showed that ABCA8 can promote the expression of sphingomyelin and sphingomyelin synthase-1 generation and maintenance. So ABCA8 is likely related to synthesis of oligodendrocyte and metabolism of myelin sphingolipid. Upregulation of ABCA8 may be a compensatory performance. Sphingomyelin is unstable and is also found in related research. The level of ABCA8 in MSA patients is directly linked to the abnormal aggregation of alpha-synuclein [32]. However, the relationship between ABCA8 and apolipoprotein has not been reported in any literature, which may be a direction of research in the future. What's more ,there are other evidences identifying that ApoE E2 allele is associated with low levels of LDL-C [33,34], which can be assumed to be a novel biomarker.

Prospect and Conclusion

Even though a novel indicator might be the serum level of cholesterol, some obstacles hold our steps to the promising future. There are many factors affecting the levels of serum lipid and nutritional status in patients with MSA. When we conduct a research, many factors should be excluded, such as Parkinson symptom caused by vascular disease, drugs and other factors of syndrome patients and have obvious lipid metabolism disorders such as liver and kidney dysfunction and some patients after hepatobiliary surgery, hypothyroidism, diabetes and ketoacidosis, serious craniocerebral trauma and surgery, tumor, cerebral infarction and other diseases of the nervous system and so on. There are still some potential factors that need to be excluded, so the results may have some bias. The study of serum lipid levels is limited to the peripheral serum now and the further confirmation of the variation of intracranial cholesterol needs to be improved, so as to provide strong evidence for the relationship between the balance of cholesterol homeostasis and the pathogenesis of MSA.

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