Review Article

Research progress on cognitive impairment and the expression of serum inflammatory markers in patients with white matter hyperintensities: a narrative review

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Background and Objective: White matter hyperintensities (WMH) are magnetic resonance imaging manifestations of brain white matter lesions, which are common in the elderly. There is a correlation between WMH and cognitive impairment, but its imaging features lack heterogeneity, which makes early diagnosis difficult. Studies have found that cognitive impairment in patients with WMH is closely related to changes in the expression of serum inflammatory markers. This article reviews the correlation between WMH and cognitive function, as well as the correlation between cognitive impairment and serum inflammatory markers in patients with WMH.

Methods: We searched the China National Knowledge Infrastructure (CNKI), PubMed, Medline and EMBASE databases to identify studies on the correlation between cognitive impairment and serum inflammatory markers in patients with WMH published between the databases' dates of inception and December 2021.

Key Content and Findings: Serum inflammatory markers such as C-reactive protein (CRP), tumor necrosis factor α (TNF-α), plasma lipoprotein phospholipase A2 (Lp-PLA2) and interleukins (ILs) are closely related to cognitive impairment in patients with WMH.

Conclusions: CRP, TNF-α, ILs and others systemic inflammatory markers can be used to help diagnose and predict cognitive impairment in WMH patients. But more in-depth and comprehensive research is needed to determine the role of systemic inflammatory markers in diagnosing WMH cognitive impairment.

Keywords: White matter hyperintensity (WMH); cognitive impairment; inflammatory markers

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Introduction

Cerebral small vessel disease (CSVD) is a kind of cerebrovascular disease whose direct cause is the damage of small blood vessels in the brain. It occurs in the elderly over 60 years old (1). There are many causes of CSVD, such as hypertension, diabetes, hyperlipidemia, smoking, and chronic obstructive pulmonary disease, among which hypertension is the most important pathogenic factor (2). The clinical manifestations of patients with CSVD are heterogeneous and occult. The main diagnostic method of CSVD is imaging examination, among which white matter hyperintensities (WMH) are one of the main imaging markers of CSVD. Magnetic resonance imaging (MRI) of the brain of CSVD patients mainly includes T2-weighted imaging (T2WI) and T2 fluid attenuated inversion recovery (T2 FLAIR) (3,4). WMH manifest as punctate, patchy,

or fusion hyperintensities in bilateral periventricular or subcortical white matter. MRI can also be used to assess the volume and severity of WMH (5,6). Studies have shown that WMH are closely related to cognitive function (7-10). The volume and severity of WMH are positively correlated with the cognitive impairment of patients with CSVD. The larger the volume of WMH, the lower the information processing speed and execution ability of patients, and the worse the overall cognition (11,12). The exact mechanism of cognitive impairment caused by WMH has not yet been elucidated, but studies have shown that inflammation is one of the key factors leading to cognitive impairment in WMH patients, including markers such as C-reactive protein (CRP), tumor necrosis factor α (TNF-α), and interleukins (ILs) (13-16). However, there are few reports on the relationship between cognitive impairment and serum inflammatory markers in patients with high white matter signal, and the conclusion is not unified. In this paper, we reviewed the research progress on cognitive impairment and the expression of serum inflammatory markers in patients with WMH, in order to provide new ideas for the prevention of cognitive impairment of patients with WMH (*Table 1*) (17-24). We present the following article in accordance with the Narrative Review reporting checklist (available at https://atm.amegroups.com/article/view/10.21037/atm-22-1016/rc).

Methods

In the present study, our primary focus was the correlation between cognitive impairment and the expression of serum inflammatory markers in patients with WMH. A literature search was performed on Dec 12, 2021 in China National Knowledge Infrastructure (CNKI), PubMed, Medline and EMBASE databases. Only papers in English and Chinese were included. Papers were considered regardless of year of publication. The following MeSH terms and their combinations were used in [tittle/abstract]: "cognitive impairment" OR "inflammatory marker" OR "inflammatory factor" OR "white matter hyperintensities". We also reviewed the related articles to broaden the scope of search. Following the database search, all identified studies will be collected, and duplicates will be removed. Subsequently, according to the inclusion and exclusion criteria, two independent reviewers will screen the titles and abstracts to assess eligibility. The search strategy summary is shown in *Table 2*.

WMH

WMH are generally located under the cerebral cortex or beside the lateral ventricle, and can manifest as high-intensity signals on T2WI or T2 FLAIR. T1-weighted imaging (T1WI) generally displays low-intensity signals, but higher than the signal intensity of cerebrospinal fluid (25,26). On MRI, WMH have two manifestations, including periventricular white matter hyperintensities (PWMH) and deep white matter hyperintensities (DWMH) (27). PWMH are adjacent to small blood vessels in the brain and have an impact on the intercortical connection fibers, while DWMH mainly appear under the cortex, affecting short subcortical fibers (28,29). Because PWMH and DWMH have different pathological characteristics and anatomical positions in the brain, they have different effects on cognitive impairment. Studies have shown that PWMH can affect the speed of onset of cognitive dysfunction, and DWMH are closely related to mild cognitive impairment (30,31). WMH mostly occur in the elderly, and the prevalence also increases with the increase of age. According to research, in people aged 80–90, subcutaneous WMH account for 100%, and paraventricular WMH account for 95% (32). The incidence rates of stroke, dementia, and mortality of the WMH population are higher than those of the normal population.

WMH and inflammatory biomarkers

Neuroinflammation can cause damage to the white matter of the brain, which in turn leads to cognitive impairment. Therefore, classical inflammatory markers, such as CRP, TNF-α, plasma lipoprotein phospholipase A2 (Lp-PLA2), and ILs, are all related to the decline of cognitive function in patients with WMH.

CRP

CRP is a protein whose plasma content rises sharply when the body is infected or tissues are damaged. CRP has the function of activating the complement system and enhancing the phagocytosis of phagocytes. It can also remove pathogenic microorganisms that invade the body, as well as damaged, necrotic, and apoptotic cells (33,34). Although CRP is not a specific marker of inflammation, it is related to the increased incidence and severity of primary stroke. In clinical practice, high-sensitivity CRP (hs-CRP) is often used as a marker of cardiovascular risk and to guide

Table 1 Characteristics of the relevant retrieved studies

Authors	Date	Number of patients	Age (years)	Study design	Condition	Results
Noble *et al.* (17)	2010	1,331	76.1 (71.5–81.0)	Cross-sectional analysis	Without dementia and available hs-CRP data and neuropsychological testing at baseline	Participants with the highest hs-CRP tertile had higher adjusted odds of impaired memory than participants with the lowest tertile. Subjects in the highest hs-CRP tertile also had greater odds of visuospatial impairment. Higher hs-CRP was not associated with executive or language impairment. Persons with at least one APOE-ε4 allele and hs-CRP in the highest tertile had the greatest odds of impaired memory
Wersching *et al.* (18)	2010	447	63.3±0.4	Cross-sectional analysis	Community-dwelling and stroke-free individuals	Higher levels of hs-CRP were associated with worse performance in executive function after adjustment for age, gender, education, and cardiovascular risk factors in multiple regression analysis. Moreover, higher hs-CRP was related to reduced global fractional anisotropy, as well as regional FA scores of the frontal lobes, the corona radiata, and the corpus callosum, in particular the genu. We did not observe a significant association of hs-CRP with measures of white matter hyperintensities or brain atrophy
Gunstad *et al.* (19)	2006	128	69.15±7.58	N/A	Documented history of CVD, Mini-Mental State Examination score of >24, no history of neurological or severe psychiatric disorders	The results suggested that CRP, but not HCY, is independently associated with cognitive dysfunction in older adults with CVD
Deng *et al.* (20)	2021	97	60.9±2.2	Retrospective analysis	All patients had WMH changes and medical records were complete	WMH patients have higher plasma Lp-PLA2 levels. Increased plasma Lp-PLA2 levels may be a risk factor for WMH associated with cognitive impairment, and it also has a higher diagnostic and evaluation value
Zhu *et al.* (21)	2019	87	N/A	Retrospective analysis	CSVD participants with MRI-determined subtypes (WMH and lacunar infarcts), likely relevant confounders of cognition or Lp-PLA2 as baseline data	Lp-PLA2 and SOD in patients with mild or severe cognitive impairment were lower than those with normal cognition. Lp-PLA2 and SOD in CSVD patients with severe WMH were significantly lower than those with mild or moderate WMH lesions
Zhu *et al.* (22)	2017	315	N/A	Cross-sectional case-control study	Complaints of memory loss and cognitive impairment on neuropsychological assessment	After controlling for covariates, higher concentrations of IL-8, but not the other measured cytokines, were associated with both CIND and AD only in the presence of significant CeVD. Subsequent multivariate analyses showed that among the types of CeVD assessed, only WMH were associated with higher IL-8 levels in CIND and AD

Table 1 (*continued*)

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Authors	Date	Number of patients	Age (years)	Study design	Condition	Results
Schuitemaker *et al.* (23)	2009	67	70.1 (63.5–76.1)	N/A	Diagnoses of MCI and probable AD, had no symptoms or signs of intercurrent infectious conditions	CSF and serum CRP levels were significantly higher in MCI compared to AD patients after adjustment for age, APOE-ε4 genotype, and cardiovascular diseases. This difference remained present in patients with a low-risk biomarker profile for AD after adjustment for the abovementioned covariates. CSF IL-6 levels were also significantly higher in MCI patients with a low-risk CSF profile
Satizabal *et al.* (24)	2012	1,841 patients	65–80	Cross-sectional analysis	N/A	In cross-sectional analyses, higher IL-6 levels were associated with higher WMH volumes and lower gray matter and hippocampal volumes, along with increasing CSF volumes in a dose-relationship pattern. Similar but weaker relationships were observed for CRP. We observed no associations between baseline inflammatory biomarker levels and the evolution of MRI findings over 4 years

AD, Alzheimer's disease; APOE, apolipoprotein E; CeVD, cerebrovascular disease; CIND, cognitively impaired no dementia; CSF, cerebrospinal fluid; CSVD, cerebral small vessel disease; CVD, cardiovascular disease; FA, fractional anisotropy; HCY, homocysteine; hs-CRP, high-sensitivity C-reactive protein; IL-8, interleukin 8; Lp-PLA2, plasma lipoprotein phospholipase A2; MCI, mild cognitive impairment; MRI, magnetic resonance imaging; N/A, not available; SOD, superoxide dismutase; WMH, white matter hyperintensity.

Table 2 The search strategy summary

Items	Specification
Date of search (specified to date, month and year)	Dec 12, 2021
Databases and other sources searched	CNKI, PubMed, Medline, EMBASE databases
Search terms used (including MeSH and free text search terms and filters)	"Cognitive impairment", "inflammatory marker", "inflammatory factor", "white matter hyperintensities"
Timeframe	From inception to Dec 12, 2021
Inclusion and exclusion criteria (study type, language restrictions, etc.)	English and Chinese
Selection process (who conducted the selection, whether it was conducted independently, how consensus was obtained, etc.)	Two independent reviewers will screen the titles and abstracts to assess eligibility
Any additional considerations, if applicable	None

treatment. Research in recent years has shown that CRP is an inflammatory marker for cognitive impairment (35). The results of Noble *et al.* (17) showed that CRP is related to memory impairment. CRP is also related to visuospatial disturbance, and the severity of the disturbance is related to the concentration of CRP. However, CRP is not related to executive dysfunction and language impairment.

Wersching *et al.* (18) studied the correlation between serum CRP and the integrity of the brain's microstructure and cognitive function. Their study included 447 patients without stroke, with an average age of 63 years and a median serum hs-CRP level of 0.12 mg/dL. The analysis results showed that the higher the serum hs-CRP value of patients, the more obvious the decline in executive function. By analyzing 219 patients with WMH, it was found that higher hs-CRP levels were associated with more WMH and less brain parenchymal volume. The research results also showed that hs-CRP can be used as a sensitive early marker of cerebrovascular diseases, but its predictive ability is poor for advanced cerebrovascular diseases. However, Gunstad *et al.* (19) analyzed 37 patients and found that CRP and WMH were not significantly related, which may be due to the small number of patients involved in the study.

Lp-PLA2

Lp-PLA2, also known as platelet activating factor acetate hydrolase (PAF-AH), is a phospholipase secreted by inflammatory cells that can promote the hydrolysis of oxidized phospholipids. It is a member of the phospholipase A2 (PLA2) superfamily (36). Lp-PLA2 is secreted by macrophages, T cells, and mast cells in the vascular intima. The expression of Lp-PLA2 is up-regulated in atherosclerotic plaques, and it is strongly expressed in macrophages that are vulnerable to the fibrous cap of plaques. Lp-PLA2 can hydrolyze the oxidized phospholipids in oxidized low-density lipoprotein (ox-LDL) to generate lipid pro-inflammatory substances (37). Studies have shown that Lp-PLA2 is involved in the pathophysiological process of atherosclerosis, and higher levels of Lp-PLA2 are related to ischemic stroke and cognitive impairment (38,39).

Deng *et al.* (20) studied the plasma Lp-PLA2 level in patients with WMH and its correlation with cognitive dysfunction. The results of the study showed that the level of plasma Lp-PLA2 in WMH patients was significantly higher than that of healthy patients, and the Montreal Cognitive Assessment (MoCA) score was significantly lower ($P<0.05$). There was no significant difference in gender, age, education level, drinking history, uric acid, total cholesterol, triglycerides, and high-density lipoprotein cholesterol between patients with cognitive impairment and those with non-cognitive impairment ($P>0.05$). However, history of hypertension, diabetes, smoking, fasting blood glucose, homocysteine, low-density lipoprotein cholesterol, and Lp-PLA2 had statistically significant differences ($P<0.05$). Logistic regression showed that fasting blood glucose, low-density lipoprotein, homocysteine, Lp-PLA2, and another four indicators were risk factors for WMH with cognitive impairment ($P<0.05$), and Lp-PLA2 had high diagnostic value for WMH with cognitive impairment [area under the curve (AUC) =0.703, 95% confidence interval (CI): 0.508–0.973; AUC =0.751, 95% CI: 0.611–0.923]. The results of the study suggest that WMH patients have higher plasma Lp-PLA2 levels, and elevated plasma Lp-PLA2 levels may be a risk factor for WMH associated with cognitive impairment, and also has a higher diagnostic value.

The results of Zhu *et al.* (21) showed that Lp-PLA2 can be used as an independent predictor of cognitive impairment in WMH patients. The possible mechanism of Lp-PLA2 leading to cognitive impairment in patients with WMH is to directly cause cognitive impairment in patients with CSVD by regulating the inflammatory damage of blood vessels and nerves in the blood circulation. Lp-PLA2 is an independent factor related to cognitive impairment in WMH, which can be used to quickly assess cognitive impairment in CSVD patients, and can also be used as a therapeutic target for cognitive impairment in CSVD patients.

IL-8

IL-8, also known as CXCL8, is a typical cell chemotactic factor that participates in and regulates numerous physiological and pathological processes. IL-8 is a cytokine secreted by macrophages and epithelial cells, and can bind to the IL-8 receptor α and IL-8 receptor β. IL-8 has a chemotactic effect on neutrophils and has a regulatory effect on inflammation. Studies have found that in patients with mild cognitive impairment and Alzheimer's disease (AD), the concentration of IL-8 in the cerebrospinal fluid will increase significantly (40,41).

Zhu *et al.* (22) showed that serum IL-8 is a marker of WMH in patients with AD. The study was a cross-sectional case-control study, including 96 patients with AD, 140 cognitively impaired no dementia (CIND) patients, and 79 patients without cognitive impairment. Blood samples were collected to measure serum IL-8 levels. The results showed that serum IL-8 levels were significantly related to patients with cerebrovascular diseases accompanied by AD and CIND. Further analysis showed that only WMH were associated with higher IL-8 levels in AD and CIND patients. The results of the study indicated that serum IL-8 can be used as a biomarker for WMH in patients with cognitive impairment and has high clinical application value.

IL-6

IL-6 is a pleiotropic cytokine that plays an important role in host defense by regulating immune and inflammatory responses. IL-6 is mainly produced by macrophages, T lymphocytes, and B lymphocytes. When the body undergoes inflammation or infection, a variety of cytokines and factors such as viruses, endotoxins, and TNF can induce the body to produce IL-6. IL-6 can also cooperate with colony stimulating factor to promote the growth and differentiation of primitive bone marrow-derived cells and enhance the lysis function of natural killer cells. Studies have shown that higher levels of IL-6 can lead to an increase in the volume of WMH (42-44). Schuitemaker *et al.* (23) showed that IL-6 is involved in the early pathological processes of WMH AD and mild cognitive impairment in patients. The study included 67 patients with mild cognitive impairment and 145 patients with AD, and measured IL-6 levels in the patients' serum and cerebrospinal fluid. The results showed that there was no significant difference in the levels of IL-6 in the cerebrospinal fluid and serum of mild cognitive impairment and AD patients. However, compared with AD patients, the level of IL-6 in the cerebrospinal fluid of patients with low-risk mild cognitive impairment was significantly increased, but there was no significant difference in the level of IL-6 in the serum.

The increase of IL-6 concentration in pregnant women will increase the risk of neurodevelopmental and mental disorders of the offspring. Although IL-6 plays an important role in the development of the fetal brain, higher levels of IL-6 may interfere with cell survival, proliferation, differentiation, and axon growth and outgrowth. Rasmussen *et al.* (45) showed that the concentration of IL-6 during pregnancy is related to the change of frontolimbic white matter and the development of cognitive ability in early life. The study has collected maternal serum samples from the first, second, and third trimesters of pregnancy to determine the level of IL-6 in the serum. The cognitive assessment of the child after birth includes sensorimotor, attention, memory, and interest and understanding of the environment. At the same time, neuroimaging data was also collected on newborns. The results of the study indicate that IL-6 levels during pregnancy are related to the cognitive development of offspring. Increased levels of IL-6 during pregnancy will affect the newborn's brain development and cognitive function (45).

Satizabal *et al.* (24) have shown that IL-6 levels are related to the severity of WMH and brain atrophy. The study included 1,841 elderly patients aged 65–80 years old, and the patients were examined by MRI and fasting serum IL-6 measurement. Through cross-sectional analysis, it was found that a high level of IL-6 in the patient's serum was related to larger WMH volume. In addition, IL-6 levels were also related to lower gray matter and hippocampal volume, as well as higher cerebrospinal fluid volume. The

results of the study show that there is a certain correlation between IL-6, WMH, and brain atrophy, which will lead to an increased risk of cognitive impairment and dementia in patients.

Other studies have shown that serum IL-1β, IL-23, IL-10, IL-21, and TNF levels are also related to WMH around the ventricle of patients with cognitive impairment (39,46-48).

Summary

WMH are MRI manifestations of white matter lesions. They are common in the elderly on cranial MRI and are the main imaging manifestation of CSVD. The risk factors of WMH include uncontrollable factors and controllable factors. Uncontrollable risk factors include age, race, gender, and apolipoprotein Eε4 allele mutations, among others (49), while controllable risk factors include high blood pressure, hyperlipidemia, fasting blood sugar, smoking, inflammation, reduced vitamin B12, and high homocysteine, among others. WMH are closely related to impaired cognitive function. Previous studies have shown that WMH are related to delayed cognitive impairment and dementia, and the severity of WMH can change the risk and progression of AD (50,51). Up to now, the specific mechanism of cognitive impairment in WMH patients has not been fully elucidated. Possible mechanisms include chronic hypoperfusion, increased permeability of the blood-brain barrier, vascular endothelial dysfunction, and inflammatory responses (52). Existing studies have shown that peripheral pro-inflammatory factors are associated with WMH, suggesting that they may be involved in the inflammatory pathway in WMH. Neuroinflammation can cause damage to the white matter of the patient's brain, which can lead to cognitive impairment. More and more evidence show that inflammation plays a vital role in the process of cognitive decline. CRP, TNF-α, ILs, and others systemic inflammatory markers are all related to cognitive decline. Since WMH imaging markers are not a single and sensitive indicator for predicting cognitive decline, systemic inflammatory markers can be used to help diagnose and predict cognitive impairment in WMH patients. However, current research results show that the sensitivity of systemic inflammation markers is not high, and some research results even demonstrate the complete opposite. Therefore, more in-depth and comprehensive research is needed to determine the role of systemic inflammatory markers in diagnosing WMH cognitive impairment.

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Footnote

Reporting Checklist: The authors have completed the Narrative Review reporting checklist. Available at https://atm.amegroups.com/article/view/10.21037/atm-22-1016/rc

Conflicts of Interest: All authors have completed the ICMJE uniform disclosure form (available at https://atm.amegroups.com/article/view/10.21037/atm-22-1016/coif). The authors have no conflicts of interest to declare.

Ethical Statement: The authors are accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.

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