

Biochemistry risk factors for ischemic stroke

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ABSTRACT

Stroke is the second leading cause of death and the third primary cause of disability in adults all over the world. The increasing incidence of stroke seriously affects the lives of patients, especially those who are disabled after stroke. It cost a lot of money for the treatment and adds a heavy burden to the families of stroke patients. Ischemic stroke patients account for the majority of stroke patients. Due to the lack of effective treatment methods for ischemic stroke, prevention is currently considered to be the best measure. Strengthening the study of the risk factors for ischemic stroke and control the risk factors to reduce the morbidity and mortality of ischemic stroke is very important. However, the studies on risk factors for ischemic stroke are limited and the researchers' views are inconsistent, the studies on some risk factors or potential risk factors for ischemic stroke didn't have an in-depth studies and lack being taking seriously. Some independent biochemical risk factors for ischemic stroke that can be applied to guide clinical work and help patients to improve their disease conditions are lacking. The article aims to summarize the biochemistry risk factors or potential biochemistry risk factors for ischemic stroke, especially those studied in recent five years, in order to help researchers to facilitate them for making further studies on exploring their association.

Keywords: ischemic stroke, risk factor, level, risk, association

INTRODUCTION

Stroke is the second leading cause of death and the third primary cause of disability in adults all over the world [1]. Ischemic stroke patients account for the majority of stroke patients, that poses a large burden to patients' families and greatly affect patients' lives. Annually, about 9.6 million people are diagnosed with ischemic stroke and out of this, stroke related morbidity is stable in developed countries, while in the developing and underdeveloped countries, it is on the rise, year by year [2]. In China, the incidence of stroke was 221/100,000 in 2007; Currently, the average morbidity due to stroke is 230/100,000, more than 3 million people are diagnosed with stroke every year - one person every ten seconds; Mortality due stroke is 132/100,000 [3]. Because lacking effective treatment methods for stroke currently, prevention is considered to be the best measure. Therefore, it is very important to control the risk factors for ischemic stroke to reduce the morbidity and mortality for ischemic stroke. We aimed to make a narrative

review to summarize the biochemistry risk factors or potential biochemistry risk factors for ischemic stroke, especially those studied in recent five years, in order to facilitate researchers to make further studies on their association.

URIC ACID AND ISCHEMIC STROKE

Uric acid (UA) is the end product of purine metabolism and is the most abundant natural antioxidant in human blood. It is the most abundant natural antioxidant in human blood and about 2/3 of all free radicals in the body can be scavenged by uric acid. In recent years, there has been considerable research into the effect of uric acid levels on the incidence and prognosis of patients with ischemic stroke, but the relationship between uric acid levels and ischemic stroke remains controversial. Some studies on uric acid and ischemic stroke indicate that uric acid is a risk factor for ischemic stroke. Bansal et al, [4] reported that stroke patients had higher levels of uric acid compared to controls. Another study in 1992 found

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lower levels of uric acid in stroke patients [5]. On the contrary, several subsequent studies reported that high levels of uric acid could increase the risk of ischemic stroke and explored gender differences and other confounding factors and use of diuretics [6]. Many studies reported elevated level of uric acid on admission increased the risk of ischemic stroke and increased the risk of early death and bad prognosis. However, these studies did not stratify the age of ischemic stroke patients. These studies only tested the levels of uric acid on admission with small sample size and did not explore the dynamic changes of uric acid's level during the disease. Zhang et al pointed elevated level of uric acid has positive association with better prognosis after discharge and thought high level of uric acid on admission played protective effect on ischemic stroke [7].

Brouns et al studied uric acid levels at 24h, 72h, 7th day, after 1 months and 3 months, and found that uric acid levels were significantly lower in the first seven days and then returned to the baseline level or above and remained so until 3 months [8]. Seet et al categorized uric acid levels in quartiles, less than 280, 280 to 340, 340 to 410 and above 410; They found that those in the fourth quartile (>410) had worse outcome, worse prognosis, higher risk of ischemic stroke, and those in the third quarter (340 to 410) had the lowest risk of ischemic stroke – a U-shaped relation between uric acid levels and outcome of ischemic stroke [9]. Other researchers studied different categorizations such as tertile, quartile and quintile, but their results are disputable and inconsistent.

Some studies indicated the elevated levels of uric acid are associated with the increased risk [10], NIHSS score, mRS score, cerebral infarct size, bad functional outcome [11], unfavorable prognosis [12], mortality [13], and recurrence of ischemic stroke as a risk factor for ischemic stroke. While other studies showed contrary results that high level of uric acid on admission provides a protective role especially in acute stroke phase and has better outcome and prognosis [14]. Lower level of uric acid foreboded worse outcome and prognosis and low level of uric acid has association with increased risk of ischemic stroke. Some researchers showed that the greater the decrease in uric acid levels after ischemic stroke, the worse the outcome, prognosis and severity of ischemic stroke, and the variation degree of uric acid levels were positively correlated with the risk of ischemic stroke in future [15]. Too high or too low of uric acid levels may be both harmful [16]. Llull et al managed to reduce the cerebral infarct sizes through supplementing uric acid to patients and combined with alteplase to treat patients [17]. In terms of the pattern of association between level of uric acid and ischemic stroke, some studies reported a U shaped [18], some reported a J-shaped [19], others linear

pattern. The influence of the uric acid levels on the incidence of ischemic stroke was inconsistent among researchers' opinions. In addition, the effect of uric acid on ischemic stroke was also inconsistent by different gender. The specific impact mechanism of uric acid levels on the risk of ischemic stroke is still not very clear. The number of existing studies on their relationship is limited, the studies of their relationship based on dynamic monitoring of uric acid levels, the stratification of uric acid levels, age stratification and in its subtypes including TIA are lacking.

HOMOCYSTEINE AND ISCHEMIC STROKE

Homocysteine (Hcy), a Sulphur-containing amino acid, is an amino acid precursor that is metabolized by methionine and cysteine methylation or sulphation and is present in small amounts in healthy individuals, and its levels can be influenced by various internal and external environmental factors. Earlier studies showed homocysteine levels have no significant relationship with ischemic stroke [20]. Then, many researchers showed that fasting homocysteine levels to be association with the risk of ischemic stroke [21], and homocysteine levels in patients of ischemic stroke were higher than the patients without ischemic stroke [22]. He et al. also reported similar findings [23]. But these researchers did not study the variation of homocysteine levels dynamically during ischemic stroke. Haapaniemi et al tested homocysteine levels on admission, 7th day, 1 month and 3 months, and showed that the levels were low on admission and then increased and remain until to 3 months [24]. Shi et al studied their association with stratification of homocysteine level in quartiles and claimed the highest quartile of homocysteine level had higher risk and mortality of ischemic stroke than lowest quartile [25]. In recent years there are more studies about the association between homocysteine level and ischemic stroke. But not many researchers studied the associations between TIA, gender, and age stratification. The results often contradict each other in terms of prognosis of ischemic stroke. Zhong et al pointed those with elevated levels of homocysteine had stronger associations with the increased risk of ischemic stroke in female than male [26]. On the contrary, Shi et al reported that the association was stronger among the males [27]. The association between homocysteine levels and the risk of ischemic stroke also differ by age [28]. Though more studies showed homocysteine levels increased with age, some studies have shown that homocysteine has no correlation with the patients' age on ischemic stroke [29]. The association between homocysteine and ischemic stroke is inconsistent between genders. The studies on their association between homocysteine

level and the risk of ischemic stroke based on different age stratification, especially in its subtypes of ischemic stroke, and gender difference are also limited.

SERUM BILIRUBIN AND ISCHEMIC STROKE

Serum bilirubin is a possible risk factor for ischemic stroke. Some studies reported elevated levels of serum bilirubin had positive association with the increased risk of ischemic stroke as a risk factor and in the severity of ischemic stroke [30]. On the contrary, other studies showed contrasting results that the risk of ischemic stroke decreased with increased serum bilirubin levels [31]. But Thakkar et al claimed elevated levels of total bilirubin has relationship with lower risk and mortality of ischemic stroke and have protective effect in stroke [32]. Choi et al also offered a contrary result to support serum bilirubin level has inverse relation with the risk of ischemic stroke and elevated levels of serum bilirubin has reduced morbidity of stroke [33]. Between genders, males with high levels of serum bilirubin levels of had higher risk of ischemic stroke [34]. As the relevant reports are very few, the effect of bilirubin levels on the risk of ischemic stroke is still unclear and very controversial. The studies on their relationship in different gender are very few, and their association among the females has not been studied.

CYSTATIN C AND ISCHEMIC STROKE

Cystatin C (Cys-C) is a product of cysteine metabolism in the body and is also known as a cysteine protease inhibitor. It is produced in the body and passes mainly through glomerular filtration, reflecting glomerular filtration function and is a stable indicator for assessing renal function. The levels of cystatin C and serum creatinine also could impact the risk of ischemic stroke as a risk factor. Earlier studies reported cystatin C had association with the risk of ischemic stroke, and cystatin C levels in patients with ischemic stroke were obviously higher than patients without ischemic stroke [35]. But there is a bit difference in another study of YANG, not only they found cystatin C is a strong risk factor and predictor of ischemic stroke whose higher levels has higher risk of ischemic stroke with cystatin C levels in quintile, but also they found cystatin C also provided an protective role in acute ischemic phase according to their mice model and humans experiment [36]. They found cystatin C increase in first three days as a response to protect brains especially after reperfusion, and then begun to decrease which is consistent with the prior study that knocking out cystatin C exacerbates the injury of brain [37]. Then Dong et al studied their association in its subtype TIA and showed cystatin-C lev-

els in TIA patients were higher than that of healthy control [38], but the studies concerned with their associations in its subtype were very few. While these studies don't notice the difference in different genders. Wang et al reported cystatin-C levels were more significantly associated with the risk of ischemic stroke in men and old people than women and the young people and high levels of cystatin C were correlated with increased risk of ischemic stroke [39]. However, there are very few studies about the association between cystatin C and ischemic stroke, the effect of cystatin C levels on ischemic stroke is not very clear. In addition, their association also needs being further studied in more detail in many other aspects such as outcome, prognosis, NIHSS score, mRS score and mortality of ischemic stroke.

N-TERMINAL PRO-B-TYPE NATRIURETIC PEPTIDE AND ISCHEMIC STROKE

N-terminal pro-B-type natriuretic peptide (NT-proBNP) is one of the fragments of brain natriuretic peptide that can be monitored and are commonly used to reflect the specifics of cardiac function. The effect of NT-proBNP on the risk of ischemic stroke has been paid more and more attention by researchers. Earlier studies showed NT-proBNP levels in the patients with ischemic stroke were higher than patients without stroke, the elevated levels of NT-proBNP had significant association with the increased risk of ischemic stroke especially in cardioembolic stroke [40]. This result was consistent in most of the earlier studies. Jensen et al also focus on monitoring the change NT-proBNP levels with testing on admission, from 2th day to 5th day, and after 6 months again and showed NT-proBNP levels obviously increased to the peak after acute ischemic stroke onset, then begun to obviously decrease and finally remain at a certain level [41]. Recent years, more studies demonstrated NT-proBNP levels had associations with cerebral infarct size, NIHSS score, mRS score, clinical outcome [42], prognosis, mortality [43], recurrence [44] and severity [45] of ischemic stroke. Zhao et al claimed elevated NT-proBNP levels could increase the death risk and bad prognosis of ischemic stroke [46]. But these studies don't focus on their relationship in its subtypes and the difference based on genders. Though Berntsson pointed NT-proBNP levels only had relationship with the elevated risk of cardioembolic stroke not other subtype [47], while Portegies et al pointed NT-proBNP had significant relation with TIA and elevated levels of NT-proBNP only could influence the increased risk of ischemic stroke in female in TIA [48]. However, there are few researches continue to further study about this problem in TIA and gender difference.

MEAN PLATELET VOLUME AND ISCHEMIC STROKE

Mean platelet volume (MPV) is an indicator of the variation in platelet size associated with platelet activation. The effect of MPV on the risk of ischemic stroke has attracted more attention among the researchers. Earlier studies showed MPV levels were associated with ischemic stroke and in predicting the prognosis of ischemic stroke [49]. However, Lok et al pointed there is no association between MPV level and the prognosis of ischemic stroke [50]. Recent studies in the last three years seem to support MPV as a risk factor for and recurrence of ischemic stroke and with the severity, mortality, and poor prognosis of ischemic stroke [51]. Inanc et al showed MPV level has significant relationship with the improvement of mRS scores in ischemic stroke during intravenous thrombolysis therapy [52]. Another study among diabetic patients showed increased levels of MPV and that diabetic patients with increased levels of MPV are prone to suffer from ischemic stroke and have high incidence rate, death rate, and serious state of illness. But these studies did not focus on their relationship in its subtype TIA and the differences between genders. Currently, only a few researches continue to study the association between MPV and TIA, and the difference between genders. However, the relationship between MPV level and the prognosis of stroke is inconsistent. The gender differences in their association have not been studied in detail. There is also a lack of studies on their association in its subtypes.

PLATELET LARGE CELL RATIO AND ISCHEMIC STROKE

Platelet large cell ratio (P-LCR) is the percentage of large platelets in the total blood platelets. Zeng et al reported that increased P-LCR could reduce ischemic stroke the rate of cerebral infarct recanalization [53]. Other study also pointed P-LCR level was higher in stroke patients than in healthy people [54], which may have a close relationship with the incidence of ischemic stroke. Almost no studies have actually examined the association between P-LCR level and ischemic stroke. And their association studies based on the P-LCR levels stratification, age stratification, different genders, and ischemic stroke subtypes hasn't been reported.

RED BLOOD CELL VOLUME DISTRIBUTION WIDTH AND ISCHEMIC STROKE

Red blood cell volume distribution width (RDW) is an objective indicator of the uniformity of the size of the erythrocyte volume. Studies have shown that RDW to be associated with of ischemic stroke, cerebral embolism and atherosclerosis. The higher levels of RDW could predict the adverse outcome of

ischemic stroke independently [55] and is associated with the occurrence of cerebral infarct. Lu et al also reported RDW as a risk factor and it could be used to predict a 3-month outcome after ischemic stroke. RDW level has a dependency with the morality for ischemic stroke [56]. Zalyesov et al also pointed that high RDW levels leads to poor recovery outcome of ischemic stroke [57]. Other studies also reported that RDW-SD levels have positive association with neuron damage in ischemic stroke patients and the RDW levels have significant association with the severity of ischemic stroke. The study by Jie Xue showed that RDW levels were correlated with the clinical outcomes and severity of ischemic stroke [58]. The RDW-CV levels are higher in the patients with stroke compared to people without stroke [54]. The studies of the association between RDW-SD, RDW-CV levels and ischemic stroke based on their levels stratification and their association in its subtypes of ischemic stroke is lacking, whether there is any difference in different genders is also not clear.

OTHER BIOCHEMISTRY RISK FACTORS FOR ISCHEMIC STROKE

Studies on levels of biochemistry indicators and ischemic stroke also reported some biochemistry indicators which were associated with the incidence, severity, prognosis and clinical outcomes, recurrence, or mortality of ischemic stroke. Urea nitrogen (BUN) with being low and high levels both had association with high risk of ischemic stroke and had relation with the prognosis of ischemic stroke. Creatinine (Cr) levels were associated with the risk of ischemic stroke, Urea nitrogen/creatinine (BUN/Cr), Uric acid/creatinine (UA/Cr) and Creatinine/Cystatin C (Cr/Cys C) were associated with the prognosis of ischemic stroke. Increased high-sensitivity C - reactive protein (hs-CRP) levels had association with the increased risk, the severity, and the functional outcomes of ischemic stroke. High-sensitivity cardiac troponin T (hs-cTnT) had close correlation with the mortality of ischemic stroke. Hemoglobin (HGB) levels were associated with short-term mortality, prognosis and recurrence. Elevated Hematocrit (HCT) levels were related to the increased risk of ischemic stroke. Albumin (ALB) levels were associated with the prognosis of ischemic stroke.

Low albumin level and low cholinesterase (CHE) level were both associated with the increased risk of ischemic stroke. High Lipoprotein a (Lpa) levels were related to the increased risk of ischemic stroke. Lower apolipoprotein A1 (ApoA1) level, elevated levels of apolipoprotein B (ApoB) and apolipoprotein B/apolipoprotein A1 (ApoB/ApoA1) were all risk factors for ischemic stroke. High D-dimer (D-D) level at admission could predict the outcomes of large vessel occlu-

sion of ischemic stroke. Glycosylated hemoglobin (HbA1c) levels could predict and were associated with the prognosis of ischemic stroke. Interleukin-6 (IL-6) was associated with the severity, prognosis and clinical outcomes of ischemic stroke.

CONCLUSION

The risk factors for ischemic stroke studied by researchers are increasing recent years, these biochemistry indicators were discovered that they may have association with the incidence, severity, prognosis and clinical outcomes, recurrence, or mortality of ischemic stroke, respectively. While some biochemistry risk factors for ischemic stroke had been studied comprehensively and deeply, some biochemistry indicators were little studied although they had been proved to have association with ischemic stroke. These risk factors especially potential biochemistry risk factors for ischemic stroke need large-scale studies and comprehensive and in-depth exploration, including studies on the short and long-term prognosis, and whether there was gender difference, the association between their levels and subtypes of ischemic stroke, measure their levels repeatedly in different time to observe levels' change in acute ischemic stroke stage, or making stratification study on their levels in ischemic stroke, in order to screen the independent risk factors for ischemic stroke to help clinical treatment and the early intervention for high-risk population, so as to reduce the morbidity and mortality of ischemic stroke.

TABLE 1. Other potential biochemistry risk factors for ischemic stroke

| potential risk factors for ischemic stroke | | | | |
|--|--|--------------------------------------|---|---|
| associated with the incidence of ischemic stroke | platelet count (PLT) | alkaline phosphatase (ALP) | Gamma-glutamyl transferase (GGT) | 25(OH)D3 |
| | lipoprotein-associated phospholipase A2 (Lp-PLA2) | insulin like growth factor-1 (IGF-1) | fibrinogen (FIB) | small and dense low density lipoprotein cholesterol (sdLDL-C) |
| | galectin-3 (Gal-3) | fibroblast growth factor 23 (FGF23) | Soluble form suppression of tumorigenicity 2 (sST2) | |
| associated with the severity of ischemic stroke | White blood cell count/ mean platelet volume ratio (WMR) | Retinol-binding protein 4 (RBP4) | Thrombospondin-1 (TSP-1) | neuron-specific enolase (NSE) |
| | glial fibrillary acidic protein (GFAP) | | | |
| associated with the prognosis and clinical outcomes of ischemic stroke | Platelet volume distribution width (PDW) | neutrophil-to-lymphocyte ratio (NLR) | platelet-to-lymphocyteratio (PLR) | triglyceride glucose index (TyG) |
| | Visinin-like protein-1 (VILIP-1) | Omentin-1 | P-selectin | |
| associated with the recurrence of ischemic stroke | β 2 microglobulin (B2-MG) | | | |
| associated with the mortality of ischemic stroke | mean corpuscular volume (MCV) | Total bile acid (TBA) | | |

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