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The Role of Hyperhomocysteinemia in the Pathogenesis of Ischemic Stroke:

A Review of Current Clinical Research

Nadia Herchi

ORCID https://orcid.org/0009-0007-9952-7222

E-mail: nadia.herchi@gmail.com

Regional Specialist Hospital in Wrocław

Henryka Michała Kamieńskiego 73a, 51-124 Wrocław - Karłowice, Poland

Knieszko Fahim
ORCID https://orcid.org/0009-0007-6320-5758
E-mail: kniecho@gmail.com
Jan Mikulicz-Radecki University Clinical Hospital in Wrocław
Borowska 213, 50-556 Wrocław, Poland

Jakub Franaszek
ORCID https://orcid.org/0009-0007-0631-9046
E-mail: franaszekjakub@gmail.com
Independent Public Health Care Centre in Kozienice, Aleja Władysława Sikorskiego 10, 26-900 Kozienice, Poland

Sara Herchi
ORCID https://orcid.org/0009-0001-4811-474X
E-mail: sara.herchi8@gmail.com
The Geneva University Hospitals, Gabrielle-Perret-Gentil 4, 1205 Geneva, Switzerland

Martyna Jabrzyk
ORCID https://orcid.org/0009-0007-7961-4986
E-mail: martynajabrzyk@gmail.com
Military Medical Academy Memorial Teaching Hospital of the Medical University of Lodz - Central Veteran Hospital, Żeromskiego 113, 90-549 Łódź, Poland

Patrycja Jarczyńska
ORCID https://orcid.org/0009-0006-7249-8276
E-mail: jarczynska.p@gmail.com
4th Military Clinical Hospital with Polyclinic SPZOZ in Wrocław 50-981 Wrocław,Rudolfa Weigla 5, Poland

Wojciech Kijowski
ORCID https://orcid.org/0009-0006-6527-9200
E-mail: kijowskiwojciech@gmail.com
Karol Marcinkowski University Hospital in Zielona Góra, Zyty 26, 65-046 Zielona Góra, Poland

Mateusz Klusek
ORCID https://orcid.org/0009-0009-0354-1527
E-mail: matyklusek@gmail.com
Ryszard Rzepka Hospital, Zwycięstwa Street 1, 66-100 Sulechów

Karolina Michalak
ORCID https://orcid.org/0009-0004-2572-976X
E-mail: michalak.karola@gmail.com
Karol Marcinkowski University Hospital in Zielona Góra, Zyty 26, 65-046 Zielona Góra, Poland

Maciej Przybył
ORCID https://orcid.org/0009-0006-1432-119X
E-mail: maciejdominikprzybyl@gmail.com
Military Medical Academy Memorial Teaching Hospital of the Medical University of Lodz - Central Veteran Hospital, Żeromskiego 113, 90-549 Łódź, Poland

ABSTRACT

Introduction. Hyperhomocysteinemia (HHcy) is often associated with the risk of stroke, which is one of the most common causes of death and disability in adults worldwide. The medical literature indicates a multidirectional effect of this amino acid on atherosclerotic and neurotoxic processes by inducing oxidative stress and promoting a prothrombotic state.The pathogenesis is further characterized by direct endothelial damage and epigenetic dysregulation. Together, these processes disrupt the structural and functional integrity of the cerebrovascular system, consequently leading to stroke.

Aim of the study. The aim of this study is to evaluate the biochemical and clinical impact of HHcy on stroke development and to assess the validity of monitoring plasma Hcy levels in patients at risk for cerebrovascular disease.

Materials and methods. The articles available in major medical databases such as Pubmed or Google Scholar are the basis of this research review. The study was conducted with the use of

keywords like ‘HOMOCYSTEINE’, ‘HIPERHOMOCYSTEINEMIA’, ‘STROKE’, ‘ISCHEMIC STROKE’.

Conclusions. Hcy is a key, modifiable risk factor for ischemic stroke that significantly worsens prognosis and leads to disability. According to the authors, the standards of neurological care should be revised to include routine monitoring of this amino acid and maintaining a level below 10 umol/L. Detecting stroke early and lowering Hcy levels in people at risk may become an important part of modern stroke prevention. However, further clinical studies are needed to confirm the long-term effect of these measures on case numbers.

Keywords: Hyperhomocysteinemia; Homocysteine; Stroke; Oxidative stress; Ischemic stroke

INTRODUCTION

Stroke is currently a major challenge for modern medicine. Although there has been significant progress in the diagnosis and treatment of the acute phase, it remains the second leading cause of death worldwide and the main factor leading to permanent disability [1]. For this reason, increasing attention is being paid to homocysteine (Hcy) – a sulfur amino acid whose role in the body goes beyond simple metabolic mediation. The metabolism of this amino acid is precisely regulated by a complex enzymatic network dependent on vitamin cofactors such as folic acid, vitamin B12, and vitamin B6 [2,3].

Understanding the pathological effects of homocysteine on the vascular system has evolved over decades. Researchers such as Anthony David Smith and Helga Refsum emphasize that elevated total homocysteine (tHcy) levels are associated with over a hundred different disease states, and their joint effect with hypertension dramatically increases the risk of vascular events [4]. The mechanisms of Hcy's harmful effects are complex and include damage to the vascular endothelium, generation of toxic oxidative stress, and unfavorable modification of protein structure, which promotes thrombus formation [2]. Furthermore, high levels of this amino acid drastically reduce the resistance of brain tissue to ischemia and intensify neuronal degeneration processes [5].

The aim of this study is to comprehensively examine the biochemical and clinical determinants of Hcy's effect on stroke pathogenesis. This study includes current knowledge of the molecular mechanisms of vascular damage, the results of groundbreaking clinical trials, and modern predictive methods to demonstrate the validity of routine monitoring of this amino acid level for prevention strategies and for personalizing treatment in patients at cerebrovascular risk.

HOMOCYSTEINE

Homocysteine (Hcy) is an endogenous sulfur amino acid, but it is not a structural protein in the human body. Systemic Hcy comes from methionine metabolism. Methionine is an essential amino acid obtained mainly from the diet [2,3]. Hcy metabolism occurs in all cells. Key transformation reactions involve B vitamins as cofactors. Deficiency in these vitamins raises Hcy levels [3,6]. Understanding homocysteine-related pathologies requires knowing its metabolic cycle. There are two key processes: remethylation with two pathways) and transulfuration [3,7]. Conversion of Hcy to methionine in the folate cycle depends on 5-mTHF as a methyl donor. Vitamin B12 and folic acid are needed for this.7 In some tissues, a folate-independent process uses betaine instead. The other main route is transsulfuration. Here, Hcy and serine form cystathionine. This reaction needs vitamin B6 [2,3,7]. Transsulfuration is irreversible and increases with high dietary methionine [3].

Normal fasting plasma Hcy concentrations are 5-15 μmol/L [7,8]. However, as indicated by more recent studies, including the 2021 Smith and Refsum consensus, values above 11 μmol/Lu in adults may already carry clinical risks [9].

HIPERHOMOCYSTEINEMIA

Hyperhomocysteinemia (HHcy) is a condition characterized by elevated blood Hcy levels. We classify it according to its severity[8]:

- mild - value between 16-30 μmol/L [8]
- moderate - values between 30-100 μmol/L [8]
- severe - values above 100 μmol/L [8]

The etiology of hyperhomocysteinemia is multifactorial and includes, among others, nutritional deficiencies, hereditary factors, and comorbidities [8].

GENETIC DETERMINANTS OF HIPERHOMOCYSTEINEMIA

The most significant cause of severe HHcy is homozygous CBS enzyme deficiency.3,10 In these patients, Hcy levels can exceed 300 μmol/l in plasma. This rare disease (1 in 200,000–400,000 people) affects many organs. Patients typically have characteristic body changes—they are tall and thin, similar to Marfan syndrome—and serious vision problems such as lens displacement [2,3,10]. A key challenge is the rapid progression of vascular changes. The disease accelerates atherosclerosis, causing early arterial stiffening and reduced lumen diameter [10]. These advanced metabolic vascular changes create a critical risk for coronary and cerebral events. They mainly determine prognosis and life expectancy in homozygotes [11]. Another, more common, genetic factor is the MTHFR gene polymorphism. Specifically, the 677C>T point mutation causes an alanine-to-valine substitution [7,12]. This variant leads to mild or moderate Hcy elevations, especially when folate is low [7,12]. Due to this mutation, Hcy cannot be effectively remethylated to methionine and builds up, particularly in the nervous system [13].

NUTRITIONAL DEFICIENCIES AND LIFESTYLE DETERMINANTS

Hyperhomocysteinemia can also be caused by a lack of cofactors necessary for homocysteine metabolism, like B-group vitamins [8]. If there is not enough of these vitamins, HCys cannot be efficiently metabolized by either remethylation or transsulfuration, leading to accumulation of Hcy in plasma. Deficits in these components in the daily diet are among the most significant factors contributing to hyperhomocysteinemia [8].

Another factor is alcohol abuse, which leads to an increase in the level of S-adenosylmethionine in the liver, which consequently stimulates an increase in homocysteine concentration [8]. This association was mostly observed in individuals with early-stage alcoholic liver disease (ALD) who have hyperhomocysteinemia [14]. An important factor that increases Hcy concentration is smoking cigarettes, which lowers the level of folates in the body [15]. Other factors correlated with increased plasma homocysteine levels include male gender, advanced age, and excessive coffee consumption [8].

COMORBIDITIES AND PHARMACOLOGICAL INFLUENCE

Numerous pathological conditions disrupt Hcy homeostasis. Renal function is critical since it influences Hcy elimination. HHcy occurs, among others, with renal failure (impaired renal

excretion and metabolism affects 85–95% of dialysis patients), diabetes, hypothyroidism, or cancer diseases such as lymphoblastic leukemia [3,9]. Some drugs are also of great importance in inducing HHcy, including methotrexate, metformin, phenytoin, and valproic acid. They affect folate metabolism and absorption [3]

MECHANISMS OF HOMOCYSTEINE TOXICITY IN STROKE

The pathogenic effects of Hcy have been widely known and studied for many years. The effect of Hcy on stroke risk is multifactorial and includes vascular damage, neurological disorders, and epigenetic changes [13,16]. The main pillars of HHcy pathogenesis are oxidative stress, endothelial dysfunction, disturbances in blood-brain barrier homeostasis, and specific protein modifications [2,8].

OXIDATIVE STRESS

A key mechanism by which Hcy contributes to stroke pathogenesis is the generation of reactive oxygen species (ROS). Homocysteine possesses a free, highly reactive thiol group (-*SH*). In the plasma and intracellular environments, in the presence of oxygen and transition metal ions, Hcy undergoes auto-oxidation, producing hydrogen peroxide (H_2O_2) and superoxide anions [2,17]. These highly reactive radicals can initiate lipid peroxidation, including the oxidation of low-density lipoproteins (oxLDL), which increases their atherogenic potential [3,16].

The oxLDL molecules damage endothelial cell membranes by sensitizing them to apoptosis. Furthermore, due to their high affinity for macrophages, they promote the formation of foam cells, a critical stage in atherosclerotic plaque development [3,16]. Additionally, Hcy may impair the body's natural antioxidant defenses. It reduces the activity of glutathione peroxidase, the enzyme that reduces lipid peroxides, and superoxide dismutase (SOD, which neutralizes superoxide radicals. This disturbance of the cellular redox potential leaves cells vulnerable to oxidative stress [3,5]

NO-RELATED ENDOTHELIAL DYSFUNCTION

The vascular effect of Hcy is primarily based on the reduction of nitric oxide (NO) bioavailability - a gaseous mediator responsible for vasodilation and the inhibition of platelet adhesion [8]. The first mechanism is linked to oxidative stress; Hcy generates free radicals that

react with NO to form highly toxic peroxynitrite ($ONOO^-$) [3,5]. Consequently, the protective effect of NO on the vasculature is limited, and vascular damage is exacerbated by nitrosative stress [3,5]. Secondly, Hcy induces the production of asymmetric dimethylarginine (ADMA), a potent endogenous inhibitor of nitric oxide synthase (NOS) [3,5]. Furthermore, homocysteine lowers the levels of tetrahydrobiopterin (BH4), an essential cofactor in NO synthesis, through reducing tetrahydrofolate - the precursor to BH4 [3,17]. A deficiency in BH4 leads to an occurrence known as NOS uncoupling. In this state, instead of producing nitric oxide, the enzyme generates additional superoxide radicals (O_2^-), creating an oxidative vicious cycle [13,17]. Additionally, Hcy stimulates the synthesis of ADMA, further acting as a natural inhibitor of NO synthase [3,16]

NEUROTOXICITY AND BLOOD-BRAIN BARRIER

Oxidative stress induced by Hcy increases blood-brain barrier (BBB) permeability, which is critical during the acute phase of a stroke [5]. Homocysteine metabolism correlates with the methylation of various amino acids, functional proteins, as well as RNA and DNA nucleotides [5]. It is hypothesized that under conditions of HHcy, modulation of gene expression occurs [5]. Research has shown that HHcy can disturb the balance between matrix metalloproteinases (e.g., MMP-9) and their tissue inhibitors (e.g., TIMP-4). This process is, in part, mediated by miR-29b, which regulates the activity of the methyltransferase DNMT3b, finally resulting in MMP-9 activation [5]. Increased MMP-9 activity degrades tight junction proteins in the cerebral microcirculation. This facilitates the infiltration of toxic molecules into the brain parenchyma and exacerbates cerebral edema [5]. Those epigenetic mechanisms explain why the effects of HHcy can persist long after an ischemic event and considerably modulate brain regeneration processes.

PROTHROMBOTIC STATE

HHcy promotes thrombus formation by activating coagulation factors V, VII, and X, while simultaneously inhibiting natural anticoagulants, such as protein C and thrombomodulin [2]. Innovative studies have identified a unique mechanism, identified as N-homocysteinylation, in which homocysteine thiolactone irreversibly modifies lysine sites in proteins, including fibrinogen [2]. This mechanism results from the oxidative modification of fibrinogen molecules by reactive oxygen species (ROS) generated during HHcy. The modified fibrinogen forms

denser fibrin networks that exhibit high resistance to fibrinolysis, significantly impairing vascular recanalization following a stroke [2,18]. Additionally, it has been demonstrated that this process induces an autoimmune response; the presence of generated anti-fibrinogen antibodies may further stabilize the clot structure [18].

MAPK SIGNALING PATHWAYS AND CALCIUM HOMEOSTASIS

Under normal conditions, ischemic preconditioning (IPC) acts as a protective function. It activates the MAPK/ERK pathway, which helps neurons survive and produce protective proteins [13]. However, HHcy impairs this natural defense. Instead of promoting survival, HHcy triggers the MAPK/p38 pathway, which leads to increased inflammation and apoptosis [13]. Additionally, HHcy interferes with calcium regulation within the cell. Specifically, it reduces SPCA1 calcium pump expression in the Golgi apparatus, which is important for maintaining ionic balance [13]. While healthy neurons use IPC to increase SPCA1 levels and survive stress, neurons in an HHcy environment are unable to adapt because this gene is silenced [13]. As a result, these cells become much more vulnerable and are more likely to die during a stroke [13].

CLINICAL ASSOCIATIONS BETWEEN HYPERHOMOCYSTEINEMIA AND ISCHEMIC STROKE

A stroke is a sudden loss of neurological function caused by vascular issues that lasts for more than 24 hours [19]. Most cases are ischemic strokes, which happen when cerebral arteries are either temporarily or permanently occluded [19]. This lack of blood flow leads to tissue necrosis and permanent damage to the neurons [19]. Acute Ischemic Stroke (AIS) is the most common form, accounting for about 85% of all cases [20,21]. From an epidemiological standpoint, stroke is the second leading cause of death and the third leading cause of long-term disability in adults worldwide [1]. Statistics show that one in four people will suffer a stroke in their lifetime [22]. In Poland, there are approximately 75,000 hospitalizations for ischemic stroke each year, with a hospital mortality rate of about 12–14% [23]. The causes of stroke are multifactorial, and scientific research shows HHcy as an important factor that increases this risk.

Clinical analyses clearly identify HHcy as an independent risk factor for the first ischemic event. A meta-analysis by Pinzon et al., which included 21 articles and 9,888 participants, showed that

Hcy levels were statistically significantly higher in stroke patients compared to the control group [24]. The authors suggest that in high-risk groups, screening for HHcy and implementing strategies to reduce Hcy levels should be considered [24]. Similar conclusions were reached by Rabelo et al. in a meta-analysis of 13 studies involving 9,947 patients [25]. However, they highlighted a very high heterogeneity between the studies [25]. This was mainly due to three specific publications where the mean differences in Hcy levels significantly varied from the rest of the results [25].

CORRELATIONS WITH ETIOPATHOLOGICAL SUBTYPES OF STROKE (TOAST)

Pathophysiological analysis proves that the diagnostic value and prognostic impact of elevated Hcy levels differ considerably depending on the primary etiopathogenetic mechanism of the stroke [26]. These mechanisms are classified according to the TOAST criteria (*Trial of Org 10172 in Acute Stroke Treatment*), a system introduced in the early 1990s during a clinical trial of the low-molecular-weight heparinoid, danaparoid [27]. The strongest and most consistent clinical correlations are observed in subtypes directly related to structural vascular changes, such as large-artery atherosclerosis (LAA) and small-vessel disease, where homocysteine promotes endothelial damage and accelerates atherothrombotic processes [28].

In their study, Zhang et al. analyzed 13 trials that demonstrated a significant association between elevated Hcy levels and ischemic stroke, including specific etiological subtypes according to the TOAST classification, in the Chinese population [28]. Clinical data indicate that Hcy levels are elevated in stroke patients when compared to healthy controls [28]. The strongest correlation with HHcy was noted in the LAA subtype, where Hcy levels were significantly higher than in other subtypes [28]. Additionally, patients with small-artery occlusion (SAO) and cardioembolism (CE) present higher Hcy levels than those with stroke of undetermined etiology (SUE) [28].

The influence of homocysteine on CE strokes remains an issue of debate. The primary mechanisms in CE, such as atrial fibrillation (AF) or intracardiac thrombi, are hemodynamic and electrophysiological processes that appear less dependent on the metabolic damage to the cerebral arterial walls [26]. However, a study by Nam et al. (2022) analyzed the impact of tHcy on functional outcomes in 910 patients with AF-related stroke. In patients with normal renal function (eGFR $\geq$ 60 ml/min/1.73 m^2), tHcy levels> 14.60 μmol/L were associated with a 3-fold increased risk of a poor functional prognosis [29]. Interestingly, no such significant correlation was observed in the renal impairment subgroup [29]. This likely reflects the fact

that Hcy is already persistently high in these patients, showing that other mechanisms prevail in these patients, and Hcy itself is constantly maintained at pathological levels [29].

HYPERHOMOCYSTEINEMIA AS A PROGNOSTIC VALUE AND RISK OF ISCHEMIC STROKE RECURRENCE

Another important correlation observed by Huang et al. was the impact of HHcy on all-cause mortality. Individuals with higher Hcy concentrations face a 1.43 times greater risk of death compared to the control group [21]. A value of 20.0 μmol/L was identified as the clinical cut-off for high mortality risk [21]. In addition, another study found that higher Hcy concentrations correlated with lower scores on the Modified Rankin Scale (mRS) - a 7-point scale assessing disability and dependence after stroke - at the 3-month post-ischemic follow-up [29]. This correlation is especially apparent in individuals with normal renal function (eGFR $\geq$ 60 ml/min/1.73 m^2), in whom an increase in tHcy was associated with a higher risk of poor outcomes [29].

Recurrent strokes account for 25–30% of all strokes, and most of these cases are, in fact, preventable [22]. Wang et al. conducted a machine learning-based study, which demonstrated that HHcy increases the risk of a recurrent ischemic event by 60% [22]. Additionally, they observed that the median Hcy in patients who experienced a recurrence was 20.7 μmol/L, compared to 14.7 μmol/L in those without recurrence [22]. These data suggest that HHcy can be considered an independent risk factor for stroke recurrence within one year [22].

CONCLUSION

Based on current scientific data, it can be concluded that Hcy represents a critical, modifiable risk factor for stroke, whose role in the body extends far beyond simple. Summarizing insights from molecular biochemistry and modern medical analytics, it is essential to point out the need to revise standards of neurological care. Routine monitoring of homocysteine levels, intended to maintain concentrations below the safe threshold of 10 μmol/L, could be an important element of modern strategies to prevent stroke. The data included in this article proves that high levels of this amino acid not only promote atherosclerotic processes, but above all drastically worsen the functional prognosis, leading to permanent disability.

Future directions of action should focus on the possible diagnosis of elevated Hcy levels in people at risk and on attempts to lower them, which could reduce the number of strokes in which homocysteine plays a key role. However, to confirm the above study results, a prospective clinical study is needed to assess the long-term association between Hcy levels and ischemic stroke.

Supplementary materials:

Not applicable.

Author's contribution:

Conceptualization: Nadia Herchi, Mateusz Klusek, Karolina Michalak; methodology: Nadia Herchi, Patrycja Jarczyńska, Wojciech Kijowski; software: Knieszko Fahim, Jakub Franaszek; validation: Maciej Przybył, Sara Herchi,; formal analysis: Karolina Michalak, Wojciech Kijowski, Mateusz Klusek; investigation: Nadia Herchi, Patrycja Jarczyńska, Martyna Jabrzyk; resources: Knieszko Fahim, Sara Herchi, Martyna Jabrzyk; data curation: Maciej Przybył, Mateusz Klusek; writing - original draft preparation: Nadia Herchi; Karolina Michalak, Maciej Przybył, Jakub Franaszek; writing - review and editing: Nadia Herchi, Mateusz Klusek, Sara Herchi; visualization: Jakub Franaszek, Knieszko Fahim; supervision: Nadia Herchi, Martyna Jabrzyk; project administration:Wojciech Kijowski, Patrycja Jarczyńska

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