Chapter 1

# Migraine and Risk Factors of Vascular Diseases

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**Abstract**

Migraine is a common neurological disease that affects both women and men in a different age. It is believed that migraine is a multifactorial disease with strong genetic and environmental factors. Current molecular studies in migraine are focused on biochemical (homocysteine, asymmetric dimethylarginine) and genetic (*ACE*, *MTHFR*, *MTR*, *MTRR*, *CBS*, *eNOS*, *NOTCH3*) risk factors associated with vascular diseases. Polymorphisms and mutations in mentioned genes predispose to migraine as well as cardiovascular diseases and stroke. According to the literature data, 13–15% of migraine with aura patients suffer from vascular diseases, too. The strict relation between migraine with aura and stroke is observed in cerebral autosomal dominant arteriopathy with subcortical infarcts and leukoencephalopathy. Lifestyle plays an important role both in the pathomechanism of migraine and vascular diseases. Hypertension, obesity, dyslipidemia, and diabetes mellitus are the important risk factors for those pathological conditions. Therefore, early diagnosis of migraine and the implementing effective pharmacotherapy can lead to the prevention of cardiovascular and cerebrovascular diseases.

**Keywords:** genetic variants, CADASIL, risk factors, cardiovascular diseases, stroke, migraine

## 1. Introduction

Migraine is a primary headache disorder and one of the most common neurological diseases because it affects 11% of the adult population worldwide. Due to clinical manifestation, the disease is divided into two main subtypes: migraine with aura (MA), the classic form, and migraine without aura (MO), the common form [1]. The exact pathomechanism of migraine remains unclear, but the new explanation underlines the neurovascular background with an

important role of trigeminovascular system and cortical spreading depression (CSD). CSD is a wave of electrophysiological hyperactivity followed by depression spreading across the cortex. This process leads to decrease in blood flow and is manifested in the aura. Migraine is a polygenetic disease with the contribution of environmental factors [2].

The most significant risk factor of migraine is gender, as migraine is more prevalent in females than in males, but a female: male ratio ranging from 2:1 to 4:1 in several populations [3, 4]. The ratio is not consistent across the age because there is no difference in the percentage of boys and girls among children aged 7–9 affected by migraine. After that age, the migraine is more common in females. The prevalence of migraine is the highest in girls after puberty and among women aged 30–50, and declines in post-menopausal period. However, the similar trend in prevalence of migraine is observed in adult men, but the absolute values are lower (**Figure 1**) [5].

Moreover, female patients with migraine are more prone to vascular diseases as compare to males. The correlation between migraine and vascular diseases, especially cerebrovascular, has been studied from ages due to similar features, such as neurovascular component, a decrease in blood flow and platelet aggregation. MA is often associated with stroke symptoms and ischemic, or rarely hemorrhagic stroke events. No such strong relation was found in MO or other headaches [6, 7]. Numerous meta-analyses underline that MA doubles the risk of ischemic stroke [8–10]. This association is stronger in younger adults, especially women <45 years of age. In the young woman with MA, the combination of smoking and oral contraceptive use has a prominent role in stroke developing [8, 9]. The high frequency of migraine attacks and longstanding history of migraine are also the risk factors for stroke [6, 11]. It may be explained by subclinical ischemic brain lesions observed in magnetic resonance imaging (MRI) of those patients [6].

The risk of ischemic stroke in migraine patients may also be increased by cardiovascular risk factors, e.g., diabetes, hypertension, obesity and dyslipidemia [12], hyperhomocysteinemia, as well as genetic factors, e.g., C677T polymorphism in *MTHFR*, insertion/deletion polymorphism in *ACE* or mutations in *NOTCH3* [13].

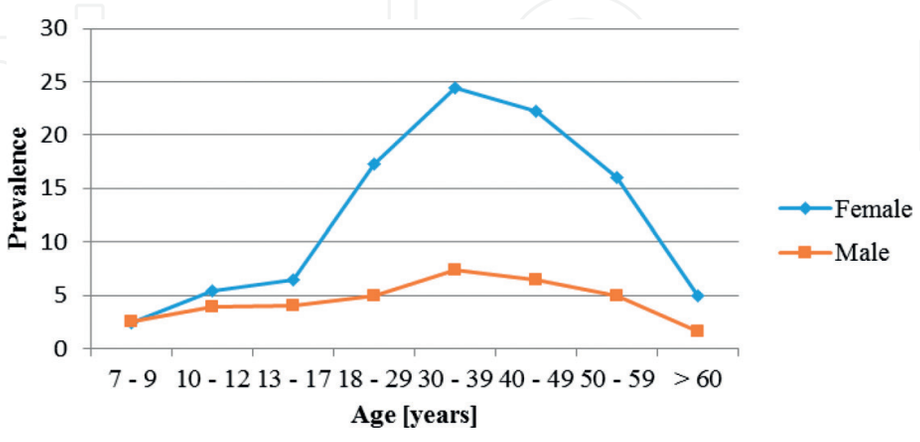


**Figure 1.** Migraine prevalence by age and sex, based on [5].

## 2. Cardiovascular risk factors

The cardiovascular diseases (CVD) and MA often coexist. The CSD involved in MA pathophysiology, migraine attacks frequency, prothrombotic effects, and impaired vascular reactivity in migraine patients or even migraine-specific treatments may increase the risk of CVD [14]. The risk factors for vascular diseases include changes in female sex hormones, hypertension, obesity, dyslipidemia and diabetes mellitus or elevated concentration of homocysteine (Hcy) and asymmetric dimethylarginine (ADMA).

### 2.1. Sex hormones

Gender differences in migraine prevalence can be explained by the influence of female hormones. Fluctuation in female sex hormones levels correlates with migraine, as attacks frequency is higher during menstruation [15, 16]. The peak estradiol level in women with menstrual related migraine is lower than in healthy group [17]. Another sex hormone, estrogen is also indirectly involved in pain transmission and pathophysiology of migraine. Additionally, estrogen, which is involved in thrombotic propensity and vasodilatory response, play the protective role against CVD risk. The CVD prevalence surges during menopause, when hormone balance is changed. This relation can explain the higher risk of CVD among younger women suffering from migraine [16].

The prospective cohort study of Kurth et al. [18] shows a consistent link between migraine and CVD events and cardiovascular mortality in women with more than 20 years of follow-up. The authors found that an approximately 50% increased risk of major CVD like myocardial infarction, stroke, coronary artery procedures, and angina pectoris. The previous study in women indicates that only MA is associated with elevated risk of CVD [14, 19]. However, in the men group, migraine is correlated with increased risk of subsequent major CVD, which was driven by the increased risk of myocardial infarction [20].

### 2.2. Hypertension

The major CVD risk is hypertension, which high appearance was found in individuals with migraine [21]. Hypertension occurs in migraine patients, both females and males, in younger age than in the non-migraine population. The 5-year prospective cohort study in Finland demonstrated that migraine is associated with an increased risk of hypertension among working-age population [22]. Among patients suffered from hypertension-migraine comorbidity the onset of both disorders occur at about 45 years of age, with the migraine starting significantly later than in only migraine patients and hypertension significantly earlier than in the hypertension-only group. Moreover, comorbidity group has a higher occurrence of the history of cerebrovascular events [23]. It is important to control hypertension in migraine and apply the proper treatment, because uncontrolled may lead to worsening of a headache and therapeutic failure. It is also crucial for the control of cerebrovascular risk, which is already increased in patients with MA [24].

### 2.3. Obesity

Modifiable risk factor for both CVD and migraine is obesity. Migraine and obesity are associated in several ways [25]. Obesity is related to higher migraine prevalence, higher attacks frequency, and also with elevated risk for developing chronic daily headache with migrainous features or transformation from an episodic migraine to chronic form [26, 27]. According to Bigal et al. [28], only 4.4% of migraneous with normal weight had 10–15 headache days per month, but percentage increases with bigger weight, in the overweight group it was 5.8%, in the obese 13.6%, and the morbidly obese 20.7%. The age and sex are also important covariates in associations between obesity and migraine [25].

The literature indicates that MA and obesity seem to be connected with CVD. It is known that such inflammatory mediators, like cytokines (interleukin 6—IL-6 and tumor necrosis factor-$\alpha$—TNF-$\alpha$), and calcitonin gene-related peptide (CGRP), which levels are increased in obese individuals, play important role in migraine pathophysiology. They may enlarge the number and duration of migraine attacks, which in turn cause central sensitization. Repeated central sensitization may be associated with neuronal damage and with poor modulation to pain. Plasma CGRP level is mostly elevated in women and its secretion can be increased by fat intake. Other peptides, the hypocretins (hypocretin-1 and -2) may also link the metabolism and pain. They control nociception and release of CGRP from trigeminal neurons. Hypocretins regulates appetite and energy metabolism: their activity is decreased in obesity. It is postulated that the dysmodulation in the hypocretinergic pathways is associated with increased susceptibility to neurogenic inflammation and migraine attacks [27, 28].

### 2.4. Dyslipidemia

Obesity is directly connected with dyslipidemia. Several studies explored the relationship between dyslipidemia and migraine in a cardiovascular context. The population-based study of men and women aged 20–65 year in the Netherlands s found that adult MA patients have "riskier" profile for CVD than MO [29]. The authors indicated that increased total cholesterol (≥240 mg/dL) and the total cholesterol to high-density lipoprotein cholesterol (HDL-C) ratio (>5) had been associated with MA. The study of Gruber et al. [30] showed that in normal weight MA patients, not only total cholesterol level is elevated, but also low density lipoprotein cholesterol (LDL-C) and oxidized LDL-C levels as compared to normal weight controls. It was demonstrated that elevated oxidized LDL-C increases the risk of migraine almost eight times. In the cross-sectional study from France, elevated levels of total cholesterol and triglycerides were associated with MA, but not with other headaches in the elderly [31]. There is also a correlation between cholesterol levels (total and LDL-C) and degree of migraine severity, with higher cholesterol values for more frequent and intense migraine attacks [32]. Moreover, the positive associations among MO, and VLDL cholesterol (VLDL-C) and remnant VLDL particles (VLDL3) were observed in women and men, respectively. VLDL is fractioned into IDL and VLDL3, which has been previously connected with higher CVD risk [33].

### 2.5. Diabetes mellitus

It is postulated that diabetes mellitus (DM) is associated with migraine, but there are conflicting results that relationship is interesting because DM affects vascular reactivity, induces neuropathy, and can be important in the pathophysiology of migraine [34]. The prospective cohort study from Finland observed that women with a headache are more often diabetic [35]. Haghighi et al. [36] showed no significant differences in the prevalence of migraine between diabetic and non-diabetic patients, these results confirmed previous study [37]. However, the authors indicated that migraine prevalence is related to the family history of migraine in the first-degree relatives, the history of hypoglycemia and durations of DM type 2. Other results demonstrated that migraine is significantly less prevalent in patients with DM than without DM [34, 38]. The study of Aamondt et al. [34] also showed that migraine prevalence is lower among patients with duration of DM ≥ 13 years or HbA1c levels >6.6%.

### 2.6. Hcy and ADMA

Hcy is an endogenous sulfur amino acid, which is formed as the intermediate product during metabolism of methionine in kidney, liver, small intestine, pancreas, blood vessels, and skin [39]. In its transformation, some enzymes and co-factors are involved, e.g., methylenetetrahydrofolate reductase (MTHFR), cystathionine beta synthase (CBS), methionine synthase (MS), also known as 5-methyltetrahydrofolate-homocysteine methyltransferase (MTR), folic acid, and vitamins B6 and B12 [40]. Increased level of Hcy (which can lead to hyperhomocysteinemia) is an important risk factor for ischemic heart disease, venous thromboembolism, ischemic stroke, and other CVD [41]. The elevated Hcy level has also been reported in patients suffering from MA [42], which may indicate an increased risk of CVD in this group. Mechanisms of adverse effects of Hcy on blood vessels are seen in the intensification of oxidative stress, reduced amount of nitric oxide (NO), the cytotoxic effect on endothelial cells, inflammation in the vascular walls, and abnormalities of the coagulation process [43]. The level of Hcy may be regulated by polymorphisms in genes encoding enzymes necessary for its metabolism, e.g., *MTHFR*, *MTR*.

ADMA is a naturally occurring amino acid, an analog of L-arginine that competitively inhibits its endothelial nitric oxide synthase (eNOS) activity, causing vasoconstriction and endothelial dysfunction leading to CVD [44]. eNOS catalyzes arginine oxidation to NO, which is one of the strongest vasodilators in the human body. Studies have confirmed that NO, changing cerebral blood flow, is responsible for migraine headaches [45]. Elevated levels of ADMA have been reported in patients with migraine compared to the control group, without any difference between MA and MO. It is interesting that the same studies also showed higher NO level in migraineurs than in control. The possible reason for increase in both ADMA and NO concentrations may be an attempt to compensate for elevated NO level and excessive vasodilatation [46]. However, there are also reports that ADMA and NO levels in migraine patients do not differ from the control group [47]. Higher concentration of ADMA may be caused by abnormalities in the function of dimethylarginine dimethylaminohydrolase (DDAH) whose role is to degrade ADMA to dimethylamine and citruline [48]. There are two forms of this enzyme: DDAH1 and DDAH2, encoded by different genes: *DDAH1* and *DDAH2*,

respectively. It was found that polymorphisms (rs233109, rs6669293, and rs12140935) in the *DDAH1* gene may influence the ADMA level [49]. The interaction among Hcy, DDAH, and ADMA was also investigated. Studies conducted on neuronal cell cultures show that DDAH inhibition by Hcy results in higher ADMA accumulation and a decrease in NO production [50]. Overexpression of DDAH protects from adverse effects for cerebral blood vessels, that results from elevated levels of Hcy [51].

## 3. Genetic risk factors

Migraine is a polygenetic disease. According to population-based family studies, MA is four-times more common in individuals with first-degree relatives suffering from MA, while the risk for MO increases two-times in terms of having first-degree relatives with MO [52]. Therefore, numerous studies investigated the association between genetic polymorphisms or mutations and MA, MO. Polymorphisms in gene coding angiotensin I—converting enzyme (ACE) and in genes related to Hcy metabolism, may increase risk both for migraine and vascular diseases. Moreover, the strict relation between migraine, especially MA and stroke, is presented in patients with cerebral autosomal-dominant arteriopathy with subcortical infarcts and leukoencephalopathy (CADASIL).

### 3.1. Angiotensin I-converting enzyme (ACE)

ACE, which is a part of the renin-angiotensin system (RAS), converts the inactive angiotensin I to angiotensin II. Angiotensin II is an active peptide responsible for vasoconstriction, regulation of blood pressure and blood volume [53]. The ACE inhibitors are used in migraine prophylaxis, and for hypertension and coronary artery disease treatment [54]. The activity of ACE may be controlled by insertion/deletion (I/D) polymorphism (rs1799752) in *the ACE* gene. The DD genotype of *ACE* I/D polymorphism is associated with the higher ACE activity, which increases angiotensin II level and in result leads to the imbalance in RAS [55]. The I/D polymorphism was linked to numerous diseases, e.g., hypertension, ischemic stroke, and migraine (MA, MO or an overall migraine, depending on the study) [56]. Thus, there is a possible association between this polymorphism, migraine, and CVD. According to Schurks et al. [57], the MA patients carrying D allele have the two-fold increased risk of CVD. The data about DD genotype and migraine attack frequency are inconsistent. Schürks et al. [58] showed that *ACE* D allele does not influence the MA or MO attack frequency while Paterna et al. [56] found that carrying the D allele determines more frequent MO attacks. The protective effect of II genotype may contribute to the reduction of the dose of ACE inhibitors in migraine prophylaxis [59].

Both polymorphisms in *MTHFR* and *ACE* genes promote oxidative stress, endothelial dysfunction and in consequence, may predispose to stroke. It was suggested that *MTHFR* C667T TT and *ACE* DD genotypes in combination might increase the migraine susceptibility, especially MA [60]; while the other study did not confirm this conclusion [61]. The meta-analysis indicated that *MTHFR* C667T TT genotype increases the MA risk, while the *ACE* II genotype protects against both MA and MO, but only in non-Caucasian populations [62].

### 3.2. MTHFR, MTR, MTRR, CBS, and eNOS

MTHFR is responsible for the conversion of 5,10-methylenetetrahydrofolate (CH2THF) to 5-methyltetrahydrofolate (CH3THF), which is a donor of the methyl group in remethylation of Hcy to methionine. Polymorphisms in *MTHFR* gene may be the reason of higher level of Hcy in blood. Fourteen rare mutations of *MTHFR* gene and one common C677T polymorphism in *MTHFR* gene were associated with severe enzymatic deficiency [63]. The *MTHFR* C677T polymorphism (Ala222Val) is associated with the decreased enzymatic activity to 30% in TT homozygous subject and 60% in individuals with CT genotype as compared to wild type genotype CC [64]. Several studies analyzed the association between *MTHFR* gene polymorphisms and migraine and obtained different results. Studies carried out in Japanese and Turkish population showed the higher frequency of TT genotype in migraine patients than in the controls [65, 66]. Moreover, Kowa et al. [65] found the particularly high frequency of *MTHFR* C677T TT genotype in MA, what correlates with results of Caucasian population studies [67, 68] reporting that TT genotype may be a risk factor for MA, but not for MO. On the other hand, studies conducted on the group of Finns excluded the association between *MTHFR* C667T polymorphism and migraine [69]. Recent meta-analyzes confirmed that the TT genotype of *MTHFR* C677T polymorphism is significantly associated with the risk of MA both in Caucasian [70] and non-Caucasian group [71] and total migraine in the non-Caucasian group [70, 71].

Another, less common *MTHFR* gene polymorphism that may be associated with migraine is A1298C (Glu429Ala). Studies by Kara et al. [66] showed that CC genotype is more common in migraine patients than in control subjects. The *MTHFR* A1296C polymorphism also reduces the activity of MTHFR without the increase in Hcy level and decrease in folate level in individuals with CC genotype. However, heterozygous patients with both *MTHFR* C677T and A1298C polymorphisms had higher levels of Hcy as compared to those who carried only C677T *MTHFR* polymorphism [72, 73].

The level of Hcy and folate may also be altered by the polymorphism in *MTR* gene encoding MTR enzyme responsible for remethylation of Hcy to methionine with the participation of vitamin B12 and 5-methyltetrahydrofolate [74]. So far, one common polymorphism A2756G (Asp919Gly), has been described in the *MTR* gene [75]. However, the effect of this polymorphism on Hcy and folate levels is not entirely clear. Li et al. [76] showed an association of *MTR* A2756G with increased Hcy and decreased folate level. On the other hand, Klerk et al. [77] denied that G allele of *MTR* A2756G affects Hcy level. Also, there was no association between *MTR* A2756G and migraine [42, 78], even in the coexistence of *MTHFR* 677CT TT genotype [79].

Another enzyme involved in Hcy metabolism is 5-methyltetrahydrofolate-homocysteine methyltransferase reductase (MTRR), encoded by *MTRR* gene. The *MTRR* A66G (Ile22Met) polymorphism may lead to elevated Hcy level [80, 81], with greater effects observed in individuals with GG genotype than GA [80]. Furthermore, the coexistence of *MTRR* A66G AG or GG genotypes with the *MTHFR* A677T TT genotype increases the adverse effect of the MTHFR variant [82].

MTHFD1 is a trifunctional enzyme composed of methylenetetrahydrofolate dehydrogenase, methyltetrahydrofolate cyclohydrolase, and formyltetrahydrofolate synthetase, encoded by *MTHFD1* gene. The most commonly analyzed polymorphisms of the *MTHFD* gene are G1958A

(R653Q) and C401T (R134K). The G1958A or C401T polymorphism individually does not increase the risk of migraine [79, 83]. However, the risk of migraine, especially MO, increases when the A allele of *MTHFD* G1958A polymorphism occurs together with the T allele of *MTHFR* C677T polymorphism. On the other hand, the group of Australian scientists found no association of *MTHFD* C401T and G1958A with the increased risk of suffering migraine [79].

CBS is an enzyme responsible for the conversion of Hcy to cystathionine, a cysteine precursor, and is encoded by *CBS* gene. Numerous genetic variants in this gene have been described, including silent polymorphisms (C699T, C1080T) [84], sense change mutations (T833C, G919A) and insertions (844ins68) [85, 86]. The most common polymorphism of the *CBS* gene, the T833C, results in the elevated level of Hcy [87] and predisposes to stroke [88]. The 844ins68 polymorphism alone does not affect Hcy plasma levels [89], whereas T833C/844ins68 induces mild hyperhomocysteinemia [90]. The occurrence of this insertion together with T allele of *MTHFR* C677T polymorphism results in lower Hcy levels as compared to the subject carrying only insertion [91]. The silent polymorphism in *CBS* gene seems to have a protective effect against CVD. Subjects with C699T TT genotype had lower Hcy level than subjects with the CC genotype [92] and consequently lower risk of CVD [93]. Also, *CBS* C1080T polymorphism leads to decrease in Hcy level, but this effect is endured by of 844ins68 mutation carriers [92]. On the other hand, the study conducted by Lievers et al. [94] showed no association between the occurrence of the silent polymorphisms and the change in plasma Hcy levels [94].

*eNOS* gene encoded endothelial NO synthase. Several polymorphisms in the *eNOS* gene were described, including T786C and G894T (Glu298Asp), but their relevance to migraine pathomechanism remains ambiguous. According to Eröz et al. [95], presentence of T alleles of *eNOS* T786C and *eNOS* G894T polymorphisms are more common in migraine patients than in controls. Other studies indicated that the TT genotype of *eNOS* G894T is associated only with a higher risk of MA [96] or there is no association [97].

### 3.3. CADASIL

The strict relation between MA and stroke was observed in CADASIL syndrome. It belongs to the group of leukodystrophies and is caused by mutations in *NOTCH3* gene [98].

CADASIL is the most frequent inherited ischemic disease of a small vessel of the brain [98]. The key features of CADASIL are MA, recurrent subcortical ischemic events and vascular dementia. The subcortical ischemic stroke is presented in 85% CADASIL patients in mean age 46 without atherosclerosis risk factors. Two of three cases are the lacunar stroke, while one of three is ishemispheric stroke. 20–40% of individuals suffer from psychiatric disorders, mostly depression or apathy. Dementia is presented in 31–60% of CADASIL patients, aged between 50 and 60, as a result of stroke history, leading to severe disability and premature death [99, 100].

Often (20–40% of cases) the inaugural symptom of CADASIL is MA started in the second–third decade of life (females: 25; males: 30–35 year of life). Interestingly, MA is five-times more frequent in CADASIL patients than in general population and may remain as the isolated symptom [100]. CADASIL patients may experience aura without a headache or atypical aura (e.g., hemiplegic, basilar, or prolonged) or even acute confusional migraine. Thus it is suggested that

atypical aura should indicate the diagnosis of CADASIL [101–104]. The frequency of MA attacks decreases after the disease progression (stroke event). Unfortunately, migraine as a common neurological disease is not a specific symptom of CADASIL, which often is misdiagnosed [100].

As mentioned before, CADASIL is a result of the mutation in the *NOTCH3* gene (19p13.12), encoding receptor protein NOTCH3. NOTCH receptors are made up of the functional extracellular domain (ECD)—containing multiple epidermal growth factor-like (EGF-like) repeats, the transmembrane domain and intracellular domain (ICD). The variants of NOTCH (NOTCH1–4) differ in the number of EGF repeats [105]. The NOTCH3 is essential for the development of vascular smooth muscle cells (VSMC) and maintenance of their function. Moreover, it protects against apoptosis and regulates the response of smooth muscle cells to external factors. NOTCH3 occurs mostly in the arteries and capillaries.

At least 200 mutations have been identified in *NOTCH3* and are located in N3-ECD. Those missense mutations create or destroy cysteine residues. As the name of disease indicates, they are inherited in the autosomal dominant pattern. *NOTCH3* consists of 33 exons, but 73% of mutations are localized in exon 4, 8% in exon 3, 6% in exons 5 and 6 [99, 106, 107]. The first step of genetic screening is analyze of exon 4, if there are no mutations the analysis is extended to exons 2, 3, 5, 6, and 11. The last step may be the screening of all exons using next generation sequencing (NGS). Different *NOTCH3* mutations were revealed among Asian of Caucasian populations [108, 109].

The CADASIL scale proposed by Pescini et al. [110] for selecting patients for genetic analysis is summarized in **Table 1**. A total score of ≥15 is an indication for genetic testing. The clinical course of CADASIL may vary between individuals with the same mutation in *NOTCH3* gene. The heterogenic manifestation of clinical symptoms makes the CADASIL underdiagnosed

| CADASIL scale | Points |
|---|---|
| Migraine | 1 |
| Migraine with aura | 3 |
| Stroke | 1 |
| Stroke onset ≤50 years | 2 |
| Psychiatric disturbances | 1 |
| Cognitive decline/dementia | 3 |
| Leukoencephalopathy | 3 |
| Leukoencephalopathy extended to temporal pole | 1 |
| Leukoencephalopathy extended to external capsule | 5 |
| Subcortical infarcts | 2 |
| Family history in at least one generation | 1 |
| Family history in at least two generations | 2 |

**Table 1.** Scale used to select CADASIL patients for genetic screening of *NOTCH3* mutations [110].

due to difficulties in distinguishing with, e.g., MA, familial hemiplegic migraine, or progressive ataxia [107]. The *NOTCH3* mutation analysis should be performed in cases with clinical features of CADASIL, even with the negative disease history.

There are two hypothesis explaining the role of *NOTCH3* mutations in CADASIL pathomechanism. According to the first of them, the mutated NOTCH3 receptor gains new functions leading to the development of degenerative changes in blood vessels. The signaling pathway is unchanged, but the cerebral blood flow autoregulation is disturbed due to the decline of VSMC functions. The persistent stress conditions lead to VSMC remodeling, reduction of cerebral vasoreactivity, the decrease in blood flow in white matter, and in consequence to chronic ischemia. The second hypothesis assumes proteinopathy as a result of N3-ECD and granular osmiophilic material (GOM) deposition in walls of blood vessels. The GOM is also presented in skin biopsy. Abnormal folded NOTCH3 protein tends to create aggregates and is not removed because of dysfunction of the ubiquitin-proteasome system. The deposition begins in 20-year-old CADASIL patients, while the changes in MRI are visible in 30-year-old patients. Interestingly, almost all CADASIL patients aged 35 with *NOTCH3* mutations have changes in MRI, e.g., white matter hyperintensities (WMH), lacunar infarcts or microbleeds. WMH lesions in T2 and FLAIR sequences may be presented even 15 years before stroke [111–113]. Four case-studies indicated that the brain MRI may be unremarkable [114].

## 4. Summary

Migraine is a multifactorial disease with both genetic and environmental background. Polymorphisms and mutations in numerous genes, e.g., *ACE, NOTCH3, MTHFR, MTR, MTRR, MTHFD1, CBS,* and *eNOS* are the genetic factors involved in its pathomechanism. Changes in biochemical parameters, such as Hcy and ADMA leading to CVD, stroke and

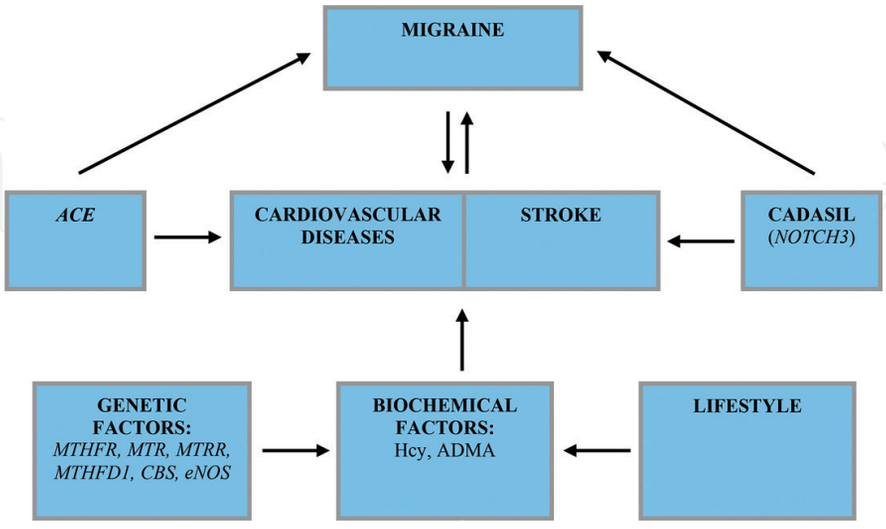


**Figure 2.** Association between migraine and cardiovascular diseases, stroke and genetic, or biochemical risk factors. ACE: angiotensin I-converting enzyme; CADASIL: cerebral autosomal dominant arteriopathy with subcortical infarcts and leukoencephalopathy; MTHFR: methylenetetrahydrofolate reductase; MTR: 5-methyltetrahydrofolate-homocysteine methyltransferase; MTRR-5: methyltetrahydrofolate-homocysteine methyltransferase reductase; CBS: cystathionine β-synthase; eNOS: endothelial NO synthase; Hcy: homocysteine; ADMA: asymmetric dimethylarginine.

migraine may be a result of lifestyle. Migraine alone can also lead to CVD and stroke. It seems that better knowledge of the migraine pathomechanism may lead to early diagnosis of migraine and the introduction of more effective pharmacotherapy and, in consequence, to the prevention of common vascular disease (**Figure 2**).

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