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Comparative study on homocysteine levels in migraine patients and normal peoples

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ABSTRACT

Migraine is known as a mysterious risk factor for ischemic stroke. Different migraine mechanisms may affect developing of so-called migraine stroke.Homocysteineis an independent risk factor for ischemic stroke. It is believed that the homocysteine level of serum is increased in patients suffering from migraine; however, the information in this field is little and non-uniform. This study aims to evaluate the serum homocysteinelevel in patients suffering from migraine as compared to healthy people. In a case- control study, 65 patients suffering from migraine and 65 normal people who were in a same age and sex with patient group were studied for 12 months in Tabriz Shams hospital and other clinics. An immunoassay method was used to measure the homocysteine level of serum after 12 hours fasting. The results from two groups were compared. Sixty five patients suffering from migraine were studied that 38.5% of them were male and 61.5% of them were female with an average age of 27.69±9.50 (15-55) years and 65 normal people, with 41.5% male and 58.5% female with an average age of 27.42±8.25 (15-52) years (p>0.05).the mean level of serum in patient group is significantly higher than the control group (averagely 14.49±5.03 against 10.92±4.68 micromole in liter; p <0.001). The difference was still remaining after sex control. The percentage of the cases that were suffering from hyperhomocysteinemia was also significantly high in the same group (61.5% against 38.5%; p=0.01; odds ratio= 2.56). Serum homocysteine level in patients suffering from migraine is significantly high than in normal people.

Key words: homocysteine, migraine, hyperhomocysteinemia.

INTRODUCTION

Migraine is a benign and recurring syndrome of headache, nausea, vomiting, and other symptoms of neurological dysfunction in varying admixtures. Clinical diagnosis of migraine is based on International Classification of Headache Disorders-II (ICHD-II) criteria specified by the International Headache Society (IHS), which classifies migraine into two major groups; without aura (MWOA) and with aura (MWA). In contrast to MWOA, MWA patients experience distinguishing neurological disturbances known as ‘aura’, which may include visual and sensory symptoms in addition to speech disturbances (1). Family and twin genetic studies demonstrate that migraine, especially MWA exhibits a genetic component (2,3). Migraine being a polygenic disorder, identification of exact genetic markers that cause or predispose to migraine is difficult due to many factors (4–6). Folate metabolism has been implicated in the pathogenesis of migraine. Two aspects are especially important in this regard; the role of

homocysteine and the status of the C677T variant of the methylenetetrahydrofolate reductase (MTHFR) gene. Since migraine is a neurovascular disease (7), the highly reactive amino acid, homocysteine has been postulated to play a role in migraine pathophysiology (4,8,9). A few studies have investigated the relationship between homocysteine and headache with conflicting results, with some showing no association and others indicating there to be an association between MWA and homocysteine only (10–14). The conclusive role of homocysteinemia in migraine is therefore yet to be settled (15).

The human MTHFR gene is on chromosome 1p36. A single nucleotide polymorphism, C677T; rs1801133) in exon 4 at codon 677 of the MTHFR gene (677C→T) causes cytosine to be replaced by thymidine, resulting in alteration in the thermolability of the MTHFR enzyme. In some populations, C677TMTHFR variant is associated with migraine (12,18–22). It would be expected to exhibit significantly reduced MTHFR enzyme activity, leading to elevation in plasma homocysteine levels (16,17), thought to contribute towards migraine susceptibility. However, the relation between the C677T-MTHFR polymorphism (leading to altered MTHFR enzyme) and homocysteine (the product of this enzyme) does not seem to follow causeand- effect rules. Many studies examining this association in various conditions have failed to confirm an association (23–27), and there is no conclusive data on this association in migraineurs.

Homocysteine is a non-protein–forming sulfur amino acid whose metabolism is at the intersection of two metabolic pathways: remethylation and transsulfuration. In remethylation, homocysteine acquires a methyl group from N-5-methyltetrahydrofolate or from betaine to form methionine. The reaction with N-5-methyltetrahydrofolate occurs in all tissues and is vitamin B12 dependent, whereas the reaction with betaine is confined mainly to the liver and is vitamin B12 independent. A considerable proportion of methionine is then activated by ATP to form S-adenosylmethionine (SAM). SAM serves primarily as a universal methyl donor to a variety of acceptors. S-adenosylhomocysteine (SAH), the by-product of these methylation reactions, is subsequently hydrolyzed, thus regenerating homocysteine, which then becomes available to start a new cycle of methyl-group transfer. It is important to note that this hydrolysis is a reversible reaction that favors the synthesis of SAH, and that elevated cellular concentrations of this metabolite are likely to precede and accompany all forms of hyperhomocysteinemia. In the transsulfuration pathway, homocysteine condenses with serine to form cystathionine in an irreversible reaction catalyzed by the pyridoxal-50- phosphate (PLP)–containing enzyme, cystathionine -synthase. Cystathionine is hydrolyzed by a second PLP-containing enzyme, cystathionase, to form cysteine and ketobutyrate. Excess cysteine is oxidized to taurine or inorganic sulfates or is excreted in the urine. Thus, in addition to the synthesis of cysteine, this transsulfuration pathway effectively catabolizes excess homocysteine, which is not required for methyl transfer.

The pathogenesis of hyperhomocysteinemia

The small amount of homocysteine normally found in the plasma is the result of a cellular export mechanism that complements the catabolism of homocysteine through transsulfuration by helping maintain low intracellular concentrations of this potentially cytotoxic sulfur amino acid. Barring kidney malfunction, the occurrence of hyperhomocysteinemia indicates that homocysteine metabolism has in some way been disrupted and that the export mechanism is disposing into the blood excess homocysteine that has accumulated in the cell. This prevents toxicity to the cell but leaves vascular tissue exposed to the possibly deleterious effects of excess homocysteine. Either a genetic defect in one of the enzymes of homocysteine metabolism or a nutritional deficiency of one or more of the vitamins that participate in homocysteine metabolism can lead to metabolic disruption and potentially to hyperhomocysteinemia. The severity and type of the resulting hyperhomocysteinemia is dependent on the extent to which the particular disturbance affects the coordination of the two pathways of homocysteine metabolism. A discussion of these disturbances follows. We investigated the role of homocysteine in this context in a pilot case-control study.

MATERIALS AND METHODS

In this case- control study, 65 patients suffering from migraine (case group) and 65 normal people (control group) who were in a same age and sex with patient group were studied for 12 months in Tabriz Shams hospital and other clinics. The homocysteine level of serum was measured after 12 hours fasting. The term of the study was 12 months and started from October of 2009. People in case group were selected according to migraine diagnosis on the basis of ICDH-H standards and being not affected with heart and renal or any other serum homocysteine level effecting diseases. Control group was consisting of normal and healthy people. Homocysteine level of serum in all

participants was measured in the morning, after 12 hours of fasting. Assessment of homocysteine level in both groups was performed in a laboratory in Shams hospital. The used kit was axis homocysteine EIA. Homocysteine levels higher than 10µ/L in women and 15µ/L in men was considered as hyperhomocysteinemia. All participants were asked to sign a written consent agreement. The investigated items included age, sex, serum homocysteine level and cases involving hyperhomocysteinemia. Statistical analysis was performed using SPSS ver. 19. Quantitative data was given as standard deviation± mean (amplitude) and qualitative information was given by frequency (percentage). For comparing quantitative data A T test was used for individual groups. To compare qualitative data K2 test was applied. For determining optimal cut-off point a ROC curve was drawn. In all cases $p<0.05$ was considered as statistical significant.

RESULTS

The average age of case group was 27.69± 9.50 (15-55) years and that of control group was 27.42± 8.25 (15-52) years. According to this, there was no statistical significant difference between two groups (p=0.86). In case group 25 patients (38.5%) were male and 40 patients (61.5%) were female and in control group 27 people (41.5%) were male and 38 people (58.05%) were female. From this perspective there was no statistical significant difference between two groups (p=0.72). The mean level of plasma homocysteine in case group was 14.49± 5.03 (3-28) µ/land that of control group was 10.92± 4.68 (2-25) µ/l. Therefore, the mean level of homocysteine in case group was significantly more than control group ($p<0.001$). The mean level of plasma homocysteine in male patients in case group was 14.48±4.26 µ/l and in female patients it was 10.59±5.45 µ/l. According to this the mean level of homocysteine in male patients was significantly higher than female patients (p=0.01). The mean amount of plasma homocysteine in female patients in control group was 14.50± 5.51 µ/l and in females of the control group the mean was 11.16± 4.46 µ/l. According to this, the mean plasma homocysteine level in female patients of the case group was significantly higher in males in control group (p=0.004). In patient group hyperhomocysteinemia was observed in 40 people and in 25 people of control group. According to this, the percentage of the cases affected with hyperhomocysteinemia in case group is significantly high than the control group (p=0.01, OR= 2.56, 95%CI: 5.18-1.27). ROC curve for plasma homocysteine level in distinction of two case and control groups is shown in. The area under mentioned curve was 0.70 with $p<0.001$. The best cut-off level in this field was calculated forserum homocysteine level≥ 12.5µ/l with sensitivity and preference of 62 and 68%, respectively.

DISCUSSION AND CONCLUSION

We found plasma homocysteine levels to be significantly associated with MWOA. Additionally, plasma homocysteine levels were lower in MWA than in MWOA. Furthermore, we did not find a relationship between homocysteine levels and the MTHFR variant (SNP rs1801133). Lastly, there may be a relationship between the MTHFR variant (SNP rs1801133) and migraine in this population. Homocysteine might have a direct role to play in migraine causation, especially keeping in view the role of homocysteine in terms of vascular damage and migraine being regarded as a neurovascular disorder (7,17). There have been studies where hyperhomocysteinemia has been shown to be associated with MWA, while a similar association has not been noted in MWOA (11). We have found increased homocysteine levels in MWOA as compared to MWA. This may indicate an ethnic difference.

An elaborate meta-analysis examining all major C677T-MTHFR related case-control studies around the world, concludes that there is no association between the said polymorphism and migraine, and that the studies included were deficient in their ethnic diversity (28). Our study is the first in this regard in Iran. Our results show a significant association of the C677T-MTHFR variant in the migraineur group ($p<0.001$) in comparison with the control group. Additionally, this significance was lost when we looked within the migraine group. In our study we only found the C/T genotype. Since our sample size is small, we cannot rule out the presence of the T/T allele in our general population these results however, can serve to form the basis of more extensive genetic studies in this population. This is important since T/T homozygosity is a recognized genetic risk factor for cardiovascular and cerebrovascular disorders (29,30). There have been studies examining the role of the C677T-MTHFR variant and corresponding homocysteine levels in various disorders (17). It is interesting to note that though altered MTHFR activity is expected to affect corresponding homocysteine levels, yet this cause and effect relationship has not been seen in many studies on various diseases (31-33). In a population-based study, Scher et al, (2006) did not find a correlation between C677T-MTHFR variant and homocysteine levels in migraine patients (20). In this study, we also did not find a significant correlation between the same parameters. Again this could mean that blood homocysteine level is

independent of the MTHFR status and/or there are other metabolic considerations that influence this correlation. We will make available more results of this study as they come in.

CONCLUSION

There is a need to replicate this study in addition to studies elucidating other aspects of homocysteine metabolism in migraine.

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