The impact of prothrombin (G20210A) gene mutation on stroke in youths

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Abstract

BACKGROUND: Stroke in young adults is a known but abnormal disease. Several recent studies have discussed the correlation between existence of coagulation factors such as V Leiden and prothrombin mutation (G20210A) as risk factors for incidence of stroke. The present study investigated the frequency of prothrombin gene mutation and its impact on incidence of ischemic stroke in Iranian youth.

METHODS: This was a case-control study using convenient sampling method on seventy six 18 to 50-year-old people provided that they did not have classical risk factors for stroke. Case group comprised 22 patients with ischemic stroke (15 males and 7 females). Fifty four healthy people (17 males and 37 females) were selected as the control group. Participants in both groups were recruited within 26 months (23.9.2007 to 21.11.2009) in Al-Zahra Hospital, Isfahan, Iran.

RESULTS: Prothrombin was not found in any of the studied patients. Heterozygous mutation was observed in one of the samples of the control group (1.85%).

CONCLUSION: Despite the known effect of prothrombin gene mutation on incidence of venous thrombosis, it does not seem this factor, as an independent factor, can be considered as a risk factor to create ischemic stroke in people who do not have other risk factor.

Keywords: Prothrombin Mutation, Stroke, Youth, Risk Factor.

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Introduction

Stroke as the third common cause of mortality in the world and a major disease leads to inability.1 The risk factors of incidence of stroke are systolic and diastolic blood pressure, hypercholesterolemia, smoking, high alcohol consumption and oral contraceptives.2 Stroke is a major cause of mortality in developed countries and it has been increased in recent decade. Unfortunately, no comprehensive study has been done in Iran in this regard; however, stroke is 33 to 43 cases per 100,000 people for Iranian population.3,4 Stroke in youths is referred to the incidence of stroke in age group under 40-45 years. It has different causes in people over 65 years. Approximately, 25 percent of stroke occurs before 65 years and 5-10 percent in ages less than 40-45 years.1 It seems that underlying cause of these infarcts can be interpreted due to some blood disorders which increase coagulability (including antiphospholipid antibodies disorders).5,6 One of the mutations associated with inherited thrombophilia is prothrombin mutation (G20210A), the second most common inherited risk factor for thrombosis which occurs in prothrombin gene. This mutation causes slightly increase of prothrombin levels higher than normal and almost increases the 2-fold risk of deep vein thrombosis (DVT) and pulmonary emboli (PE).7 It seems this mutation does not create any functional difference in prothrombin molecule. Moreover, increased level of prothrombin does not have much difference compared to healthy people that prepare ground for necessarily measuring it. Therefore, the involvement of the prothrombin mutation in thrombus formation is unclear. Detection of G20210A genotype by DNA analysis was confirmed in terms of this specific mutation. The present study investigated the impact of prothrombin gene mutation (G20210A) on incidence of ischemic stroke in the youths in Iran.

Materials and Methods

This was a case-control study on 76 people including 32 males (42.1%) and 44 females (57.8%) ranged 18 to 50 years of age, which was done from 23.9.2007 to 21.11.2009 in Al-Zahra Hospital in Isfahan. Twenty two patients under 50 years with ischemic stroke were selected as case group and 54 healthy people under 50
years also as control group using convenient sampling method. The control group included 37 and 17 females and males respectively. They were healthy normal peer who had no history of known cardio ischemic diseases, diabetes, hypertension and cerebrovascular diseases. The case group included 15 males and 7 females who had been selected among twenty two 18-50 year-old patients admitted in neurology ward of Al-Zahra Hospital after diagnostic tests of ischemic stroke and/or TIA. In the first stage, the patients with history of cardiovascular and valvular heart diseases, hypertension, diabetes mellitus, smoking and alcohol consumption, hyperlipidemia, malignancy and chronic renal diseases were excluded. All the patients underwent electrocardiography in order to rule out cardiac source of stroke. Trans-thoracic and trans-esophageal echocardiography (if necessary) were conducted in order to examine myocardial dyskinesia, valvular problems and probable vegetations. Doppler sonography of carotid artery was done in order to examine stenosis is or dissection. Examining the possibility of coagulopathy was done with coagulation factors including antithrombin II, protein C, S and also antinuclear antibody (ANA), antineutrophil cytoplasmic autoantibody (ANCA), antiphospholipid antibodies and anticardiolipin antibody for ruling out the vasculitis. Twenty two patients diagnosed with no underlying risk factors and enrolled in the study. After obtaining their consent, whole blood sample was taken from all the patients in tubes containing EDTA which initially the DNA was extracted from the white blood cells and then they underwent PCR-RELP surgery and finally the type of gene polymorphism was identified.8

Results
After conducting the gel electrophoresis, prothrombin mutation (G20210A) was found in none of the patients. Heterozygous prothrombin mutation (G20210A) was found in one of the subjects of the control group (a 37-year-old woman with no history of thromboembolic disease). No case of homozygous mutation was found in this group. Considering a case of mutation in healthy samples, the frequency of prothrombin mutation (G20210A) was calculated 1.85%. There were not significant differences in frequency of Prothrombin mutation between case and control groups (P > 0.05).

Discussion
The present study was the first study in Iran to evaluate the impact of prothrombin gene mutation (G20210A) as an independent risk factor in incidence of ischemic stroke. After reporting the cause of prothrombin gene mutation (G20210A) in 1994,9 several studies examined its effect on coagulation disorders. Considering the known effect of this mutation on developing venous thrombosis, several studies were designed to evaluate the prevalence of it in various races and communities including Iran. The next step was investigating the possible role of this mutation in arterial vascular events. Several case-control studies assessed the existence of prothrombin gene mutation (G20210A) in patients with myocardial infarction and ischemic stroke and its comparison with control group.10,14 In the present study, exclusion of patients with classical risk factors for stroke, made it more possible to judge about the pathogenicity of this mutation. In addition, since there was no similar study for the prevalence of this factor in Esfahan Province, this case-control study provided an estimation of it in healthy population of this province. The frequency of 1.85% which was obtained in our study was in accordance with studies which discussed the higher prevalence of this mutation in Caucasians; the theory which says this mutation has been derived from the Middle East, and then spread to Western and North Europe.14 According to studies in different nations, variable prevalence has been reported for this mutation. Accordingly, the prevalence of this gene is varied from 3.1% in Sweden,13-15 1.8% in Germany to 0.5% in Serbia.16 This mutation has a low prevalence in East Asia such as Thailand, China, Korea and Japan and also Africa.16-19 The obtained relative frequency in this study in comparison with its high prevalence in Turkey (2.6%) in North West of Iran in the one hand, and its near-zero frequency in east Asian courtiers and east parts of Iran on the other hand, placed Iran in the middle of an intermediate region with high prevalence and areas with low prevalence of this mutation.

Prothrombin gene mutation (G20210A) were not found among the 22 studied samples. Therefore, to some extent this study can be in accordance with many studies which mentioned that existence of prothrombin gene mutation (G20210A) has no role in increased arterial thrombosis risk factor.17,18 However, some studies even have found a strong correlation between the existence of prothrombin gene mutation (G20210A) and incidence of myocardial infarction.

Despite the known effect of prothrombin gene mutation (G20210A) on incidence of venous thrombosis, this mutation is considered as a relatively weaker risk factor in incidence of thrombotic events. The present study provided data that the pathogenicity of this factor could be analyzed. A case-control study20 which was done on American female youths with myocardial infarction made a 25-fold risk
for them who were prothrombin gene mutation (G20210A) carrier in addition with smoking. The women, who had this factor but did not smoke, had no higher risk compared to others. Not finding the prothrombin gene mutation (G20210A) in our selected patients made us realized that this mutation perhaps can increase the risk of stroke in terms of hypertension, diabetes mellitus or other stroke risk factors and cannot be a potential risk by itself; a finding which was confirmed by other studies.\(^{20,21}\)

**Conflict of Interests**
Authors have no conflict of interests.

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