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Short Communication

Testing for Thrombophilic Disorders in Young Adults with Ischemic Stroke or Transient Ischemic Attack

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Abstract

Young adults aged 50 years and below with ischemic stroke or transient ischemic attack have significantly different risk factors from older stroke patients. As a result, they are often worked up extensively to evaluate for the underlying cause of the stroke. The aim of this retrospective study at our hospital was to determine how often tests for thrombophilic disorders are ordered for such patients and the yield of such tests. The results of this study showed that thrombophilic tests were frequently ordered by neurologists but the yield from such tests was low.

Keywords: Cryptogenic stroke; Thrombophilic disorders; Young stroke; Ischemic stroke

Introduction

Close to 40% of strokes in young adults are cryptogenic [1]. Thrombophilic disorder testing is frequently done when the usual cardiovascular risk factors are not present. However, the yield and utility of doing extensive thrombophilic disorder testing in these patients can vary among populations [2]. Singapore is a Southeast Asian country that has a mixture of different races, predominantly Chinese, followed by Malays, Indians and Eurasians.

Thrombophilic disorders can be inherited or acquired. Factor V Leiden, Protein C deficiency, Protein S deficiency and Antithrombin III deficiency are inherited thrombophilic disorders that are commonly tested for in young ischemic stroke patients [2,3]. However, these disorders are more frequently associated with an increased risk of venous thrombosis and the utility of testing these in arterial ischemic stroke patients is controversial.

Antiphospholipid syndrome is an acquired autoimmune thrombophilic disorder that can be associated with both arterial and venous thromboses. The presence of lupus anticoagulant or anticardiolipin antibodies in stroke patients suggest the possible diagnosis of antiphopholipid syndrome but these tests can sometimes be falsely positive in the acute phase of stroke. Therefore, these tests have to be repeated at least 12 weeks after the stroke to determine if the patient truly has antiphospholipid syndrome.

Elevated plasma homocysteine levels have been reported in some studies to convey a higher risk for thrombotic events [4]. Homocysteine levels can be elevated due to a mutation in the 5,10-Methylenetetrahydrofolate Reductase (MTHFR) gene or can be due to a nutritional deficiency in vitamin B6, vitamin B12 or folic acid. However, the utility of replacing these vitamins remains controversial and a randomised placebo-controlled trial showed no difference in incidence of cardiovascular events in the group that was given daily vitamin B6, vitamin B12 and folic acid [5].

In addition, the costs of these thrombophilic disorder tests can be substantial, costing more than 1000 US dollars in the United States and 500 US dollars in the United Kingdom [6].

The aim of our study was to determine how often neurologists at our institution order such thrombophilic disorder testing when managing young adults with ischemic stroke or TIA and the yield of such tests.

Methods

We retrospectively reviewed anonymised data from 276 consecutive patients aged 50 years and below that were admitted to our hospital in Singapore between January 2016 to October

2017 for either ischaemic stroke or transient ischaemic attack. All these patients had been evaluated and treated by our neurologists. The etiology of the stroke was classified according to the Trial of Org 10172 in Acute Stroke Treatment (TOAST) criteria [7] and extent of investigations for the etiology of stroke were determined by the managing neurologists. These investigations could include but were not limited to screening for thrombophilic disorders, such as Factor V Leiden, Protein C deficiency, Protein S deficiency, Anti-thrombin III deficiency, anticardiolipin antibody, lupus anticoagulant and fasting homocysteine levels. This study was approved by our country's National Healthcare Group's Domain Specific Review Board.

Results

Of the 276 patients in our study, 67% were of Chinese ethnicity, 15% of Malay ethnicity, 11% of Indian ethnicity and 7% of other ethnicity. 58.5% of the patients had strokes that were classified under large vessel atherosclerosis, cardioembolism or small vessel occlusion using the TOAST criteria. 41.5% of the patients in our study had strokes that fell into "stroke of other determined etiology" or "stroke of undetermined etiology". Various thrombophilic disorder tests were ordered by the managing neurologists to workup the etiology of the stroke as shown in Table 1.

Thrombophilic disorder test	Number of patients who had the test done (% of total young stroke/TIA patients)	Number of patients with positive test results, (% of total young stroke/TIA patients)
Factor V Leiden	68 (24.6)	1 (1.5)
Protein C	37 (13.4)	1 (2.7)
Protein S	36 (13.0)	0 (0.0)
Anti-thrombin III	45 (16.3)	0 (0.0)
Anti-Cardiolipin antibody	191 (69.2)	5 (2.6)
Lupus anticoagulant	180 (65.2)	0 (0.0)
Fasting homocysteine	151 (54.7)	28 (18.5)

Table 1: Various thrombophilic disorder tests.

Among the thrombophilic disorder tests, the most commonly ordered test was Anticardiolipin antibody (69.2%). This was followed by Lupus anticoagulant (65.2%), fasting Homocysteine levels (54.7%), Factor V Leiden (24.6%), Antithrombin III (16.3%), Protein C (13.4%) and Protein S (13.0%).

The test with the highest number of positive results in our study was the fasting homocysteine level. Elevated fasting homocysteine levels were found in 28 patients. This constituted 18.5% of all the patients in this study. 5 patients tested positive for anticardiolipin antibodies (IgM or IgG). Only 1 patient tested positive for Protein C deficiency and 1 patient tested positive for Factor V Leiden. No patients in this study tested positive for Protein S deficiency, antithrombin III deficiency or lupus anticoagulant.

The only patient who tested positive for Protein C deficiency had concurrent deep venous thrombosis of his lower limb and a patent foramen ovale. The cause of his stroke was determined to be likely due to thromboembolism across the patent foramen ovale and that the Protein C deficiency had likely caused the deep venous thrombosis of his lower limb. The only patient who tested positive for Factor V Leiden was of Middle-Eastern origin and had a strong family history of stroke.

Discussion

Young adults with ischemic stroke or transient ischemic attack have more varied stroke etiologies compared to the older age group and require more extensive testing to determine their stroke etiology [8]. Tests for thrombophilic disorders are frequently ordered in this group of patients despite the low yield as was seen in our study. The test with the highest yield in our study was the fasting homocysteine level test but the significance of lowering the homocysteine levels to reduce recurrent stroke risk has been controversial [5,9]. The inherited thrombophilic disorders (Factor V Leiden, Protein C deficiency, Protein S deficiency and antithrombin III deficiency) were rare in our study population and the only patient who was detected to have Protein C deficiency had concurrent deep venous thrombosis, which is consistent with the literature that these inherited thrombophilias are more commonly associated with venous thromboses [10].

Given the low yield of such tests, larger studies should be done to determine the cost-effectiveness of ordering such tests in young adults with ischemic stroke or TIA and to identify subgroups of patients who may benefit more from having these tests.

Disclosures

The authors have no conflicts of interest to disclose.

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