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SCREENING FOR THROMBOPHILIA IN STROKE: ARE WE OKAY?

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ABSTRACT Stroke is now a global epidemic. It is on the rise, especially among the young population. The mechanism of stroke needs to be determined for appropriate management. Unfortunately, 40 percent of young strokes have an unknown aetiology. So, we should not leave any stone unturned to find a possibility to treat. Thrombophilia in stroke is one such condition and is still a neglected entity in many parts of the world. Clinicians need to remember the appropriate time to test, the methodology, standard laboratory values, and the selection of patients for lifelong anticoagulation. In the absence of definitive data, it should be practised to obtain testing for hypercoagulable conditions in patients who have a personal or family history of systemic thromboses, no clear aetiology for ischemic stroke or transient ischemic attack (TIA), and clinical findings that suggest systemic lupus erythematosus or the antiphospholipid antibody syndrome.

KEYWORDS : Ischemic stroke, Thrombophilia, Stroke in young

Stroke is now a global epidemic. It is the major cause of disability worldwide and the second leading cause of death. [1]

Stroke in young is an on rise in every corner of the world. The incidence rate of young stroke calculated in their study was very high (46/100,000).[2] So, we should not leave any stone unturned to find a treatable opportunity to determine stroke aetiology and specify treatment. However, almost one–fourth of ischemic strokes are cryptogenic. [3] And almost 40% of strokes in young adults have unknown aetiology. [4]

We deal with common markers of thrombophilia which are related to vascular events, especially stroke in our day-to-day practice. However, there lies a lack of definite guideline / recommendation in testing and interpretation of the results of these costly markers of thrombophilia. Thrombophilic factors have been implicated in 4-8% of the young strokes worldwide. [5] So, we should excavate this modifiable risk factor of stroke and thereby prevent future strokes, as anticoagulation is an important option in these patients.

The pre-test probabilities of coagulation defects in the patients with ischaemic strokes are:

Lupus anticoagulant: 3 percent (8 percent in patients ≤50 years)
Anticardiolipin antibodies: 17 percent (21 percent in patients ≤50 years)

Activated protein C resistance/factor V Leiden mutation: 7 percent (11 percent in patients ≤50 years)

Prothrombin mutation 5 percent (6 percent in patients ≤50 years).

Amongst the markers of thrombophilia, Factor V Leiden, Protein C deficiency, Protein S deficiency, Antithrombin III deficiency, Prothrombin gene mutation, Antiphospholipid antibody, hyperhomocystenaemia have an important relationship with stroke.

A brief discussion about them:

Factor V Leiden

Because of mutation in *F5* gene, Factor V Leiden (FVL) results. The *F5* gene encodes the factor V protein of the coagulation cascade. FVL renders factor V protein insensitive to the actions of activated protein C, which is a natural anticoagulant. So, people with FVL variant are at increased risk of stroke and venous thromboembolism.

In a small series of patients (younger individuals less than 60 years, women, and smokers) were found to be at increased risk for pro-thrombotic state. [6,7,8,9]

Protein S deficiency

Protein S serves as a cofactor for activated protein C, which inactivates procoagulant factors Va and VIIIa, reducing thrombin generation. Protein S also serves as a cofactor for activated protein C in enhancing fibrinolysis and can directly inhibit prothrombin activation via interactions with other coagulation factors. In a series of 127 consecutive patients admitted for an acute ischemic stroke, abnormally low levels of protein S were found in four (3 percent). [10]

In another series of 120 patients with cerebral ischemic events, 20 (17 percent) had decreased protein S levels, but on repeat testing protein S levels were only low in two (2 percent). [11]

Protein C deficiency

Protein C circulates as a zymogen and exerts its anticoagulant function after activation to activated protein C (aPC), a serine protease. The primary role of aPC is to inactivate coagulation factors Va and VIIIa, which are necessary for efficient thrombin generation and factor X activation, respectively.

Ischemic stroke has been reported in young adults (heterozygotes) with hereditary protein C deficiency. [12,13,14]

Antithrombin III

Antithrombin (AT, previously called AT III, also known as heparin cofactor I) is a natural anticoagulant. It inhibits thrombin (factor IIa), factor Xa, and other serine proteases in the coagulation cascade, such as factor IXa.

A deficiency of plasma antithrombin III has been identified as a potential risk factor for thrombosis. In a pilot study of 56 patients aged less than 40 years who presented with an ischaemic stroke of unknown aetiology, only one case of plasma antithrombin III deficiency was detected.[15]

Prothrombin gene mutation

The mechanism by which prothrombin G20210A increases the risk of thrombosis is incompletely understood but is thought primarily to involve an increased concentration of prothrombin in the circulation, possibly by increased efficiency of prothrombin mRNA 3'-end formation and increased prothrombin biosynthesis without affecting the rate of transcription; increased glycosylation that promotes protein stability may also play a role.

In a meta-analysis, the mutation was associated with significantly increased stroke risk in adults less than 55 years.[16]

Antiphospholipid antibodies

A large prospective study showed that antiphospholipid syndrome manifests as stroke and TIA in 2.4% and 2.3% of cases, retrospectively. [17]

There are three types of APA with different phospholipid binding sites: lupus anticoagulant (LA), anticardiolipin antibody (ACL) of IgG or IgM subtype, and anti-β2 glycoprotein 1 (anti-β2GPI) of IgG or IgM subtype. Among APAs, the specificity of arterial thrombosis is higher for LA and anti-β2GPI. [18]

Interpreting positive APA results in stroke requires careful consideration of antibody type, isotype, and titre in the clinical context.

Hyperhomocysteinemia

Increased serum homocysteine concentrations are associated with an increased risk of coronary and cerebrovascular disease. Elevated homocysteine appears to be associated with an increased risk of the large artery subtype of ischemic stroke, and possibly to the small artery subtype; it does not appear to be associated with cardio embolic or other stroke subtypes. [19,20]

The tests for thrombophilia evaluation need to be performed at least three months after the acute illness, as acute inflammation will influence the results.

For patients undergoing testing and on anticoagulation, it is preferred that all tests be performed a minimum of two weeks following discontinuation of anticoagulation, when workable. Although not all tests are affected by acute thrombosis or anticoagulants (clinical setting and anticoagulant that interfere with thrombophilia are: protein C deficiency, protein S deficiency, anti-thrombin deficiency, lupus anticoagulant) this approach avoids repeated testing, erroneous test results, and recurrent hospital visits.

There is a high possibility that there lies racial variation in positivity of individual titres of thrombophilia factors. The positive titre which correlates with the vascular event needs to be individualized in each group of population. So that interpreting the result is reliable.

The cost of the investigation needs to be rationalized in developing and underdeveloped countries, so that it can be done overcoming financial resistance.

It is quite possible that thrombophilia factors, even while positive in low titres, can precipitate vascular event when patient is exposed to pro-thrombotic state like surgery, pregnancy, infection, and while on pro-thrombotic drugs like steroid, chemotherapeutic agents. So even positivity of the factors in low titres needs to be interpreted with caution because they may precipitate catastrophic life-threatening vascular events.

In the absence of definitive data, it should be practiced to get testing for hypercoagulable conditions in patients who have:

1. A personal or family history of systemic thromboses
2. No clear etiology for ischemic stroke or transient ischemic attack (TIA), despite cardiac and vascular imaging, especially when involving young patients
3. Clinical findings that suggest systemic lupus erythematosus or the antiphospholipid antibody syndrome.

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