The role of coagulopathies in stroke

Coagulopathies cause a predisposition to thrombosis and therefore an increased risk of ischaemic stroke. Although the frequency of coagulopathies in patients with stroke is low, the yield for diagnosing coagulopathies is typically greatest in young patients, those with family history of thrombosis, those with repeated unexplained strokes and patients with no vascular risk factors, as Omer H T Ali with Drs Bella Richard and Pradeep Khanna explain.

Sroke is defined as a focal (or at times global) neurological impairment of sudden onset, and lasting more than 24 hours (or leading to death) and of presumed vascular origin. Cerebral ischaemia accounts for 85 per cent of presentation and primary intra-cerebral haemorrhage for 15 per cent. Coagulopathies have been implicated in one to four per cent of ischaemic stroke. Disorders of coagulation may occur as a result of an alteration in the amount or function of the protein cascade due to either congenital or acquired aetiologies. This causes a predisposition to thrombotic events (hypercoagulable state) and, therefore, an increased risk of ischaemic stroke. Thrombosis can be divided anatomically into venous and arterial thrombosis. The inherited hypercoagulable syndromes primarily affect veins, and only rarely causes arterial thrombosis. The acquired hypercoagulable states, such as the antiphospholipid antibody syndrome, are more implicated in arterial stroke. The aim of this article is to provide a detailed review of the literature to date on the role of coagulopathies in arterial and venous thrombosis.

Arterial thrombosis

Antiphospholipid antibodies: anticardiolipin antibodies (ACL)/lupus anticoagulant (LA)
Antiphospholipid antibodies (APL) are a heterogeneous family of antibodies that react to negatively charged membrane-bound phospholipids or phospholipid-protein complexes. Even though antiphospholipid antibodies are associated with both arterial and venous thrombosis, they are more commonly implicated in arterial stroke. The prevalence of APLs has been estimated to occur in two to seven per cent of the normal population. However, there is an increased prevalence with age, rising to 51.6 per cent among patients aged between 67 and 95 years. Among patients with APL, 20 per cent present with stroke. Several controlled studies of ACL or LA found a significant association with ischaemic stroke. Brey et al, reported detectable levels of APL in 21 of 46 (46 per cent) subjects under 50 years of age presenting with stroke or TIAS, compared with only two of 26 (eight per cent) in controls. The association between

Table 1. Association of coagulopathies with arterial and venous thrombosis

<table>
<thead>
<tr>
<th>Coagulopathy</th>
<th>Arterial</th>
<th>Venous</th>
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<tbody>
<tr>
<td>Antiphospholipid antibodies</td>
<td>++++</td>
<td>+</td>
</tr>
<tr>
<td>Hyperhomocysteinemia</td>
<td>+++</td>
<td>+</td>
</tr>
<tr>
<td>Sickle cell disease</td>
<td>+++</td>
<td>+</td>
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<tr>
<td>Factor V Leiden</td>
<td></td>
<td>+++</td>
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<tr>
<td>Antithrombin deficiency</td>
<td>+</td>
<td>+</td>
</tr>
<tr>
<td>Protein C / S deficiencies</td>
<td>+</td>
<td>+</td>
</tr>
<tr>
<td>Prothrombin gene mutation</td>
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ACL/LA and ischaemic stroke is well known in patients with antiphospholipid antibody syndrome and systemic lupus erythematosus\(^4\). APL patients tend to have a high stroke recurrence rate, those who present with arterial stroke are also likely to have recurrent arterial stroke\(^5,2\). Despite the strong association between APL and stroke, the precise mechanism by which they promote thrombosis remain unknown. Many problems exist in interpreting the reported studies, including the lack of standardisation of laboratory tests or criteria for a positive result.

**Hyperhomocysteinemia**

Hyperhomocysteinemia is now recognised as a risk factor for arterial disease, including carotid artery stenosis and stroke\(^1\). The pathogenesis of homocysteine-induced arterial disease is not well elucidated, however several mechanisms have been proposed including: an increase in adhesiveness of platelets; activation of the coagulation cascade; conversion of low density lipoprotein (LDL) cholesterol into proatherogenic forms; and endothelial damage with increased tissue factor expression\(^6\). It has also been suggested elevated levels of homocysteine increases the odds of carotid intimal thickening by more than threefold\(^7\). A case-controlled study suggested as many as 30 per cent of subjects with ischemic stroke had higher homocysteine levels compared with the controls\(^8\). Clarke R et al reported 42 per cent of stroke patients had elevated levels of homocysteine\(^9\). In another meta-analysis 11 of 27 studies concerned with cerebrovascular diseases, concluded elevated levels of homocysteine is an independent risk factor for stroke\(^10\). Supplemental folate, and to a lesser extent vitamin B6 and vitamin B12, can lower serum homocysteine levels, and vitamin supplementation is currently being investigated as a preventive treatment for patients with elevated homocysteine levels at risk for arterial disease\(^1\).1.

**Sickle cell anaemia**

Stroke is common in patients with sickle cell anaemia. It has been suggested 10 per cent of individuals with HbSS (sickle cell anaemia) and two to five per cent of those with HbSC (haemoglobin-sickle cell disease) will experience symptomatic stroke, and an additional 13 per cent may develop asymptomatic stroke\(^12\). As sickle cell disease develops, there is a progressive narrowing of the distal internal carotid artery, portions of the circle of Willis and proximal branches of the major intracranial arteries\(^13\). Sickle cell plugging of microcirculation and cerebral veins can also occur\(^1\).2. Blood transfusion is the mainstay of treatment and is highly effective in reducing the risk of stroke\(^1\).3. Untreated patients tend to have an exceptionally high stroke recurrence rate of 67 per cent, compared with 10 per cent in those receiving frequent transfusion\(^1\).4.

**Venous thrombosis**

*Factor V Leiden mutation (FVL)*

By far the most common inherited disorder leading to venous thrombosis is the clinical syndrome of activated protein C (APC) resistance caused by the mutation in factor V (factor V Leiden)\(^1\). A single point mutation (G to A transition of nucleotide 1691) in exon 10 of factor V gene leads to the substitution of arginine 506 by glutamine (factor V Leiden) and results in a factor V molecule that is resistant to cleavage by APC\(^1\). This mutation is present in the majority of the patients with activated protein C resistance. Resistance to APC or factor V Leiden has been estimated to occur in two to 15 per cent of Caucasians\(^1\). Molecular studies have shown that FV Leiden homozygotes are exposed to a higher risk of thrombosis, an eightyfold increase compared with heterozygotes at a sevenfold increased risk\(^1\). A study of 19 patients with cerebral venous thrombosis has reported an incidence of factor V Leiden in 21 per cent\(^1\). In another study of families with factor V Leiden, the risk of thrombosis in asymptomatic carriers has been estimated to be one per cent per year between the ages of 20–50 years compared with 0.1 per cent for those without the mutation\(^1\). Notably several case control and prospective studies have failed to find evidence of a significant association between factor V Leiden mutations and arterial stroke\(^1\),\(^1\).2.

*Antithrombin III deficiency (AT)*

Antithrombin inhibits thrombin and factors X, IXa, Xla, XIIa and Kallikrein by forming an irreversible complex\(^1\). There are two major types of antithrombin deficiency. Type I is characterised by a quantitative reduction of functionally normal antithrombin protein. Type II is due to the production of qualitatively abnormal protein. In both types antithrombin activity is reduced to a variable extent\(^1\). Type II is further stratified according to the molecular defect: reactive site (thrombin binding site); heparin binding site; and pleiotropic effect (characterised by multiple functional defects)\(^1\). The distinction between the subtypes of antithrombin is of clinical importance as the incidence of thrombosis is higher in association with type I deficiency (relative risk
cent, type II deficiency in where mutation affects the reactive site. The prevalence of antithrombin deficiency in the general population is 0.18 per cent. In studies of patients with ischaemic stroke, antithrombin deficiency was reported in 0.2 per cent. While the prevalence of protein S deficiency remains unknown, protein C deficiency in the general population has been estimated to occur in 0.2 per cent. In studies of patients with ischaemic stroke, protein C deficiency was reported in 1.4 per cent and protein S in 0.9 per cent. Even though venous thrombosis has been well documented as being caused by abnormalities in protein C and protein S, evidence supporting the role of deficiencies in protein C and protein S in arterial infarction are limited.

Prothrombin gene mutation
Prothrombin is the final step in fibrin formation. Mutation in prothrombin gene leads to a gain of function of prothrombin and hence an increased risk of venous thrombosis. Even though several studies have shown an association between the prothrombin gene mutation and venous thrombosis, there is no compelling evidence indicating this mutation is a significant cause of arterial stroke.

Prognosis and despite an increased risk for thrombosis, the prognosis of most hypercoagulable states is

References

excellent and currently there is no data showing increased mortality with protein C, FVL or AT deficiency compared with the general population\textsuperscript{36}. However, presentations associated with increased mortality include cerebral venous thrombosis and ischaemic stroke. The optimal management of a patient with a hypercoagulable state after a single episode of venous or arterial stroke is unknown\textsuperscript{39}. In patients with acquired coagulopathy, treatment of the underlying conditions may reverse the risk. In patients with hereditary deficiencies, and those with recurrent ischaemic episodes, warfarin is often recommended\textsuperscript{36}. Levine et al, investigated the efficacy of warfarin compared with aspirin for thrombosis prevention in subjects with antiphospholipid antibodies. They concluded that there was no significant difference in stroke recurrence between those receiving aspirin or warfarin\textsuperscript{40}. In order to identify the risk reduction with specific therapy, there is a need for more randomised control trials comparing long term anticoagulation to oral antiplatelet therapy in patients with coagulation disorders.

**Conclusion**

The role of coagulopathies has been well established in arterial and venous thrombosis leading to ischaemic stroke. However, because of the low frequency of coagulopathies in patients with stroke, it is difficult to justify screening all stroke patients. Specialised coagulation testing may be beneficial in young patients, those with a family history of thrombosis, those with repeated unexplained strokes and patients with no vascular risk factors. Additional prospective controlled studies of stroke patients are necessary to assess the prevalence rates and to further increase our knowledge of the role of coagulopathies in the aetiology of ischaemic stroke.

*Conflict of interest: none declared.*