CASE REPORT

Combined deficiency of proteins C and S: ischaemic stroke in young individuals

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SUMMARY

In adults of any age, the majority of strokes are ischaemic (caused by a blockage in the blood supply to the brain). Stroke in young individuals poses a major health problem. The WHO defines stroke as an event caused by the interruption of the blood supply to the brain, usually because of rupture of a blood vessel or blockage by a clot. This hampers the supply of oxygen and nutrients, causing damage to the brain tissue. Globally, stroke is the third commonest cause of mortality and the fourth leading cause of disease burden. Ischaemic stroke is the most common cerebrovascular disease, most often due to atherothrombotic diseases and uncommonly by disorders of hypercoagulation. Disorders of coagulation leading to thrombotic disorders are approximately 1% of all ischaemic strokes and 4–8% of strokes in young individuals. Similarly, combined deficiency of proteins C and S can lead to hypercoagulable state and rarely presents as a cerebrovascular accident. We describe here a case of a 25-year-old man who presented with right middle cerebral artery territory infarct due to protein C and S deficiency.

BACKGROUND

Cerebrovascular diseases are one of the common causes of high morbidity and mortality all over the world and among all cerebrovascular diseases, most common being ischaemic stroke (85%).^{1–3} Stroke in young individuals poses a major problem, as these young family members are the major bread earner of the family. Abraham *et al*⁴ from Vellore, South India reported that 25% of cases of stroke occur in less than 40 years of age. Other Indian studies have highlighted a higher incidence (24–35%) of stroke in young population.⁵ Atherothrombotic diseases are the most common cause of ischaemic stroke; however, disorder of coagulation, although uncommon, can lead to hypercoagulability resulting in ischaemic stroke.

CASE PRESENTATION

A 25-year-old man was admitted in King George Medical University, Lucknow, Uttar Pradesh, India, in 2012 with symptoms of weakness in the left half of the body, slurring of speech, deviation of angle of mouth towards the right side while talking, along with difficulty in deglutition and drooling of saliva from the left side for 10 days. On inquiry, no risk factors such as smoking, obesity, diabetes, hypertension and valvular heart disease were found. Family history was negative for other vascular events or any predisposing factors for stroke.

On examination, general examination was unremarkable and all peripheral pulses were normal. Nervous system examination showed normal higher mental function, and speech was dysarthric. Cranial nerve examination showed left-sided upper motor neuron type of facial palsy along with absent gag reflex towards the left side. Power was decreased in the left upper and lower limb (III/V). The rest of the systemic examinations were within normal limit.

INVESTIGATIONS

On routine investigation, haemoglobin was 13 gm/dL, total leucocyte count 12 000/dL, platelet count 1.52 lac/mm³ with haematocrit of 39%, erythrocyte sedimentation rate 28 mm, prothrombin time 13 s (control 12 s), International Normalised Ratio 1.1 and activated partial thromboplastin time 22 s (control 20 s). Urine analysis, chest X-ray and fundus examination were unremarkable. Kidney and liver function tests were within normal range. Ultrasonography of the abdomen and continuous wave Doppler sonography study of the carotid, vertebral arteries and all four limbs were normal. Transthoracic and transoesophageal echocardiography did not reveal any abnormalities. Protein C level was 38 units/mL (normal 67–195 units/mL), protein S level was 20 units/mL (normal 55–123 units/mL) and antithrombin III (AT III) level was 88 units/mL (normal 70–122 units/mL). Serum homocysteine level, lipid profile, antinuclear factor and antiphospholipid antibodies were within normal limits. Factor V Leiden mutation was not detected. CT of the brain was performed which showed a large wedge-shaped hypodense area

Figure 1 CT scan showing infarct in the middle cerebral artery territory region.

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Figure 2 Brain CT showing infarct in the right frontotemporal region.

suggestive of infarct in the right frontotemporoparietal region (figures 1 and 2).

DIFFERENTIAL DIAGNOSIS

- ▶ Cardioembolism
- ▶ Arterial dissection
- ▶ Vasculitis/antiphospholipid antibody syndrome
- ▶ Thrombophilia
- ▶ Premature atherosclerosis

TREATMENT

After initial therapy with heparin, the patient was kept on warfarin for long-term treatment (anticoagulation), which was started at a low dose and was gradually increased.

OUTCOME AND FOLLOW-UP

The patient was discharged from the hospital in good condition after 2 weeks and was followed up to 3 months.

DISCUSSION

Ischaemic stroke is uncommon in young age, and despite extensive investigations a large proportion of ischaemic strokes are of undetermined aetiology. Stroke means different pathological processes, ultimately leading to focal cerebral ischaemia. Eighty-five per cent of the strokes are ischaemic and 15% are haemorrhagic. Even among the patients with ischaemic stroke, a number of different pathological processes, such as cardioembolism, large artery disease with arteriolosclerosis and thromboembolism and small artery disease, are responsible. Young ischaemic stroke attracts a barrage of diagnostic tests, mainly searching for an underlying thrombophilic state. The importance of thrombophilic disorders in arterial stroke has been debatable.

Thrombophilic disorders can be broadly divided into two groups: inherited and acquired condition. Inherited thrombophilic disorders are far less commonly observed in young ischaemic strokes. These are caused due to deficiencies of natural anticoagulants such as protein C, protein S and AT III deficiency, polymorphism causing resistance to activated protein C (factor V Leiden mutation) and disturbance in the clotting balance (prothrombin gene 20210 G/A variant). Of all the inherited thrombophilic disorders, factor V Leiden mutation is perhaps the commonest cause, accounting for about half of the cases. Prothrombin gene mutation, protein C, protein S deficiency and antithrombin deficiency account for most of the remaining cases. On the contrary, acquired thrombophilic

disorders are more common such as the antiphospholipid antibodies syndrome, associated with lupus anticoagulant and anticardiolipin antibodies.

The factor V Leiden mutation, the cause of activated protein C resistance (in 90% of cases), is the most common inherited coagulopathy associated with stroke. Antithrombin deficiency has only rarely been associated with stroke. Protein C is a vitamin K-dependent plasma protein that acts first as an anticoagulant, by proteolytically degrading the activated factor V and inactivating factor VIII, and thereafter facilitates thrombolysis by its fibrinolytic activity. Protein S serves as a cofactor for protein C in its anticoagulant properties.⁶ Protein C deficiency has been associated occasionally with arterial ischaemic stroke.⁷ The relevance of deficiencies of these naturally occurring anticoagulants for venous thrombosis or pulmonary embolism is well established. There are conflicting reports from India as well as other countries, thereby limiting the reliability of the association between protein C deficiency and arterial ischaemic stroke.^{8 9} We report an unusual case where protein C and protein S deficiency resulted in arterial ischaemic stroke.

The significance of the coagulation inhibitor deficiencies in the aetiology of ischaemic stroke is controversial. Hart and Kanter¹⁰ concluded that the aetiological association of protein C deficiency and protein S deficiency is controversial. In our case, antithrombin deficiency and factor V Leiden mutation were absent. Thus, the evidence linking antithrombin deficiency with arterial stroke is weak. Deficiency of both coagulant inhibitors in the same patient may strongly predispose for arterial thrombosis resulting in cerebral ischaemia. On the basis of available data, special laboratory screening for prothrombotic states contributing to stroke is recommended only for selected patients. The cause and imminent precipitant of ischaemic strokes remain unexplained in many patients. The potential contributory role of prothrombotic states warrants further investigation.

Learning points

- ▶ Dealing with a case of cerebral infarction with few risk factors for arteriosclerosis, the screening for thrombophilia should be performed, especially when the patients are below 45 years of age, having a personal history of recurrent thrombosis without precipitating factors, such as thrombosis at unusual sites, thrombosis during pregnancy and a positive family history of thrombosis.
- ▶ A positive result demands initiation of adequate anticoagulant treatment.

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Competing interests None.

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