CASE REPORT

DEFICIENCY OF PROTEIN S AND FACTOR V PRESENTING AS ISCHEMIC STROKE IN A 14 YEARS OLD BOY

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ABSTRACT

A 14 year old nondiabetic, nonhypertensive boy was admittedwith left sided hemiparesis. He has been diagnosed with ischemic stroke due to combined deficiency of protein S and factor V.Inherited thrombophiliadue to deficiencies of natural anticoagulants (antithrombin, protein C and protein S) and activated protein C resistance (APC-R) are more commonly associated with venous rather than arterial thrombosis. While deficiency of factor V leads to heamorrhage, some mutations like factor V Leiden predispose for thrombosis .Combined deficiency of both protein C and factor V leading to arterial thrombo-embolism causing ischemic stroke is a rarer event.

Key words: Ischemic Stroke,Stroke in young , Thrombophilia

INTRODUCTION

Though the specific definition of "young stroke" is lacking, the vast majority of authors consider young stroke to pertain to individuals under 45 years of age. Stroke incidence rises steeply with age, therefore, stroke in younger individuals are less common. The cause of ischemic stroke in young adults are many and diverse. The principal cause of stroke in young are due to extra cranial arterial dissection, cardioembolism, premature atherosclerosis, migraine, drugs, thrombophilias, anti phospholipid antibody syndrome, vasculitis, pregnancy and genetic disorders.[1] Such patients usually require more extensive investigations in order to find an underlying cause than more elderly patients. Stroke in young individuals can be devastating in terms of productive years lost and the impact on a young person's life. It is important that a comprehensive search is made since many of the underlying disorders are treatable.

CASE REPORT

A 14 year old boy suddenly developed weakness of left upper and lower limbs and was admitted in our hospital. There was no history suggestive of sensory loss, bowel or bladder involvement. He had no complain of fever, headache, loss of consciousness or convulsions. There was no past history of cardiac disorder, joint pain, skin rash. His birth was by normal delivery and there was no delay in achieving developmental milestones. Patient gives no history of smoking or drug abuse.

On examination, patient was conscious. Pulse was 84 beats per minute, regular rhythm, all peripheral pulses were palpable and no bruit was heard over any artery. Nervous system examination revealed normal higher functions and cranial nerves. Motor examination showed hypotonia of the left upper and lower limb with grade 0/5 power in both left limbs which gradually improved during the hospital stay to 4-/5 in left upper limb and 4+/5 in left lower limb. All deep tendon reflexes were exaggeratedon the left side with an extensor planter response on the left side. Sensory and cerebellar functions were normal. Cardiovascular system examination did not reveal

any abnormality and all other systemic examinations were normal.

Investigation results are as shown in table.

Table 1: Report of Investigations

Investigations	Report
Haemoglobin	11.1gm/dl
white blood cell count (WBC)	4500cmm (N_{72} L_{26} M_{01} B_{00} E_{01})
ESR	40mm in 1 hr
Peripheral smear	normocytic normochromic
BT (bleeding time)	1'30"
CT (clotting time)	4'35"
Cholesterol	142md/dl
Triglyceride	161mg/dl
Hdl-C	45mg/dl
Vldl-C	32mg/dl
Ldl-C	65mg/dl
ASO (anti streptolysin O)	301 IU
Bilirubin (total)	1.1mg/dl (conjucated-0.6, unconjugated-0.5)
Total protein	7.1mg/dl
Serum albumin	4.2mg/dl
Alanine amino transferase	21U/L
Aspertate amino transefe-rase	24U/L
Alkaline phosphatase	172U/L
Homocysteine	14.34 (5.4-16.20) micromoles/L
Factor V	37 (70-120)
Protein C	106 (70-140)
Protein S	17 (60-140)
Urea	24mg/dl
Creatinine	1.0mg/dl
LDH	435
Uric acid	3.9
ANA in hep 2 culture	Negative
Echocardiography	LVEF- 60% Rest within normal lin
Chest roentgenogram	Within normal limits
Mantoux test	Negative
MRI brain	Altered intensity in right sided ganglia and periventricular region diffusion restriction

DISCUSSION

The diagnosis was pretty evident from the clinical examination,but the main problem was finding the etiology. Uncrossed complete hemiparesis suggests a lesion at the basal ganglia. No history of loss of consciousness, no features of raised intracranial tension excludes haemorrhage. Sudden onset weakness developing within seconds suggests an embolism leading to cerebral infarction, which was confirmed by magnetic resonance imaging of brain. (Figure 1)

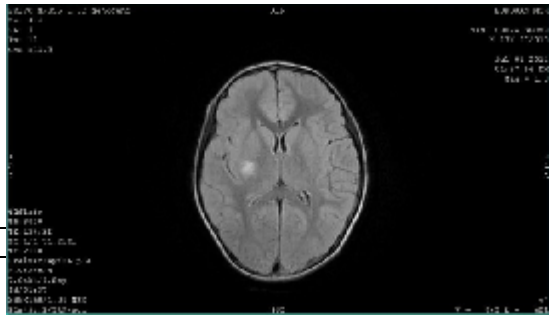

Figure 1: MRI Brain T2 FLAIR showing infarct in the right basal ganglia

There was no carotid bruit. The echocardiogram, electrocardiogram and lipid profiles were normal. No source of embolism could be found. On further investigating, Protein S and Factor V were found to be deficient. He was advised to take warfarin with regular follow up with prothrombin time - INR.

Inherited thrombophilia is more commonly associated with venous rather than arterial thrombosis. There is controversy regarding the role of inherited causes of thrombophilia such as deficiencies of natural anticoagulants (antithrombin, protein C and protein S) and activated protein C resistance (APC-R) in arterial thrombosis, while increased fibrinogen levels and acquired causes such as antiphospholipid antibodies have been implicated.[2] (Figure 2)

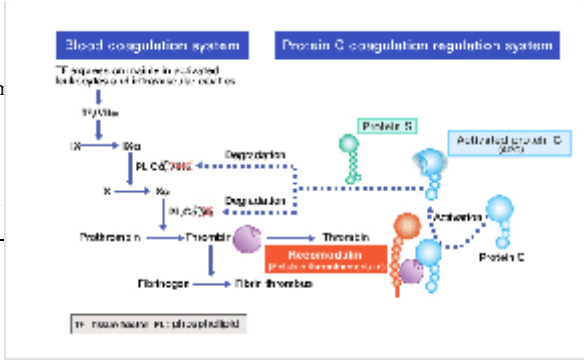

Figure 2: Coagulation Cascade

While deficiency of factor V leads to heamorrhage, some mutations like factor V Leiden predispose for thrombosis. The most common cause for thrombophilia is factor V mutation. The most common among them, factor V Leiden mutation is due to replacement of an arginine residue with glutamic acid

at amino acid position 506. This mutant factor V escapes degradation by activated protein C (APC) leading to a prothrombotic state.Factor V Leiden mutation is autosomal dominant. Interestingly, factor V Leiden heterozygotes who carry a null mutation on the counterpart (non-Leiden) factor V allele not only have reduced plasma factor V levels (~50%), but also show an APC resistance phenotype comparable to that of factor V Leiden homozygotes. This rare condition, known as pseudohomozygous APC resistance,[3-4] is attributable to nonexpression of the non-Leiden factor V allele and consequent absence of normal factor V in plasma. Thus this shows an association of Factor V deficiency with factor V Leiden mutation.

In our case, we find a deficiency of protein S which produces aprothrombotic state, in association with a deficiency of factor V which is a pro hemorrhagic state. The boy had an cerebral infarction, suggesting that either the effects of factor S deficiency over powers those due to deficiency of factor V or factor V deficiency is associated with mutation of factor V. Contrary to the previous belief that factor V Leiden is rare in Indians,[5] some recent studies have reported higher frequency of APC-R in Indian patients with venous thrombosis.[6-8] Due to the paucity of funds, the patient could not be tested for genetic mutations.

We would like to report this case due to its rare combination of protein S and factor V deficiency leading to arterial thrombosis rather than venous thrombosis. We would also like to conclude that every young patient with ischemic stroke without any cardiovascular disorder should be investigated for a hypercoagulable state so that they may be put on anticoagulants for the rest of their life to prevent recurrences. But because of the costly investigations, it is often difficult for physicians of developing countries like ours.

REFERENCES

1. Martin PJ, Enevoldson TP, Humphrey PR. Causes of ischaemic stroke in the young. Postgraduate Medical Journal. 1997;73(855):8-16.
2. Mishra MahendraNarain, Kalra Ravi, RohatgiShalesh. Clinical profile, common thrombophilia markers and risk factors in 85 young Indian patients with arterial thrombosis.Sao Paulo Med. J. [Internet]. 2013 [cited 2015 June 30] ; 131(6): 384-388.
3. Greengard JS, Alhenc-Gelas M, Gandrille S, Emmerich J, Aiach M, Griffin JH. Pseudo-homozygous activated protein C resistance due to coinheritance of heterozygous factor V-R506Q and type I factor V deficiency associated with thrombosis [abstract]. ThrombHaemost1995*;* 73*:* 1361.
4. Simioni P, Scudeller A, Radossi P, et al. "Pseudo homozygous" activated protein C resistance due to double heterozygous factor V defects (factor V Leiden mutation and type I quantitative factor V defect) associated with thrombosis: report of two cases belonging to two unrelated kindreds.ThrombHaemost1996*;*75*:* 422*-426.*
5. Wolf M, Boyer-Neumann C, Martinoli JL, et al. A new functional assay for human protein S activity using activated factor V as substrate. ThrombHaemost 1989;62(4):1144-5.
6. Herrmann FH, Salazar-Sanchez L, Schröder W, et al. Prevalence of molecular risk factors FV Leiden, FV HR2, FII 20210G>A and MTHFR677C>T in different populations and ethnic groups of Germany, Costa Rica and India. International Journal of Human Genetics. 2001;1(1):33-9.
7. Bhattacharyya M, Kannan M, Chaudhry VP, Saxena R. Venous thrombosis: prevalence of prothrombotic defects in north Indian population. Indian J PatholMicrobiol 2003;46(4):621-4.
8. Saxena R, Mohanty S, Srivastava A, Choudhry VP, Kotwal J. Pathogenetic factors underlying juvenile deep vein thrombosis (DVT) in Indians. Eur J Haematol 1999;63(1):26-8.