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A Rare Genetic Disorder of Protein C Deficiency Induced Acute Ischemic Stroke in Young Adult

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Abstract **Case Report**

The liver produces the 62-kD vitamin K-dependent glycoprotein known as protein C (PC) as a zymogen. PC is activated by attaching to the thrombin-thrombomodulin complex, with protein S (PS) serving as a cofactor. Among its numerous functions, PC functions as a naturally occurring anticoagulant. A homozygous or heterozygous deficiency places the individual at risk for thrombosis, specifically venous thromboembolism, and causes major events like myocardial infarction (MI), deep vein thrombosis, pulmonary embolism, or a fatal stroke. A 21yrs male patient came to ER department with the chief complaints of Giddiness, Chest pain, seizures, and 2 episodes of vomiting with elevated blood pressure 200/140 mmhg. He had no past medical history; Patient CT scan of brain showed normal findings But MRI revealed acute infarcts in brain. Also reduced protein c functional activity, Normal Protein S, Increased WBC count and increased APTT levels. All other laboratory investigations were normal. Patient was treated with antihypertensive, Antiplatelet, Anti-hyperlipidaemias drugs, eventually patient vitals became normal and discharged.

Keywords: Protein C, Protein S, APTT, Acute Infarct, Chromogenic and Clot based assays.

1. INTRODUCTION

PROTEIN C DEFICIENCY

The liver produces a 62-kD glycoprotein called protein C, and that is dependent on vitamin K. It is an inactive zymogen that travels through the blood vessels. When PC links oneself to the endothelium proteoglycan thrombomodulin, thrombosis catalyses the changing of PC into the serine-protease-like enzyme known as activated PC. APC's anticoagulant role includes the inactivation of blood coagulation factors Va and VIIIa, which are essential for factor X activation and thrombin production. PC utilizes a nutrient K-dependent protein S as a cofactor. A low PC puts a person at risk for thromboembolism by changing the ratio between pro coagulant and anticoagulant proteins [1]. Natural anticoagulants play a critical function in eliminating the adverse effects of pro coagulant proteins and platelet phospholipids being exposed to the vessel wall for a longer amount of time because of the reduced flow of blood velocity in the venous circulation. In events with PC deficiency, it may help to explain the increased risk of pulmonary embolism, vein thrombosis in the legs, and venous thromboembolism at youthful ages. Although arterial thromboembolism and PC deficit seem to be related, the exact cause behind this link is still up for disagreement. If PC is not replaced, the extremely uncommon homozygous forms may exhibit severe thromboembolic consequences that lead to neonatal purpura fulminans, a potentially deadly disease marked by skin necrosis and microvascular thrombosis. Low antigen and activity levels are two characteristics of type I PC deficit (quantitative defect). On the other hand, type-II defects only show low PC activity levels (qualitative deficiency) and normal PC antigen levels. Type I inadequacies are more prevalent (75–80%) than type II deficiencies (20–25%) in VTE patients. Antigen and functional tests are the two primary categories of PC assays. Immunoassays known as antigen assays are made to quantify the amount of PC, independent of its purpose. Type II deficits won't be found if just an antigen assay is conducted [2]. Thus, the first screening test ought to be a functional assay. An antigen assay may be considered to identify the kind of deficiency if a low result is obtained. Assays for PC activity can be chromogenic or clot-based. A snake venom activator is used in both clot-based and chromogenic assays to change the patient's plasma PC into APC. APC subsequently breaks down factors Va and VIIIa in a clot-based assay, extending the clotting time based on aPTT or RVVT. APC's capacity to cleave

a synthetic substrate and release a chromogenic product that can be detected spectrophotometrically is assessed by chromogenic assays; however, these tests do not evaluate all of PC's functional domains. As a result, chromogenic assays may have higher PC levels than clot-based assays. However, compared to a clot-based assay, a chromogenic assay reduces intra-laboratory and inter-laboratory variation when measuring PC activity. DNA sequencing for genetic analysis may be used to find PC mutations [3].

DIAGNOSIS

Functional tests are widely utilized in diagnostic testing for protein C deficiency. There are multiple accessible chromogenic tests for protein C that apply activation by snake venom in an activating reagent (Protac; Ankara Corp, Mason, OH, USA). Further offered for sale are clotting assays and enzyme-linked immunosorbent assays. After acute consumptive contexts have resolved and when oral antibiotic therapy is not being applied, retesting of individuals with low protein C levels is advised in order to rule out an impending deficit due to the occurrence of acquired short comings. To know if protein C deficiency is acquired or congenital, patients with APA and low protein C levels can be analyzed for antiprotein C antibodies. Sample collection, assay performance, and interpretation (i.e., preanalytic and analytic conditions) quality assurance difficulties are essential [4].

TREATMENT

1. Moderately Poor in PC

Most patients with acute thrombotic events are dealt with the same initial treatment when they occurred in patients with mild PC lack of it. The kind of thrombotic difficulties and its location define the course of treatment. While oral anticoagulation is gradually started, heparin therapy is initially started and maintained for patients with venous thrombosis, such as DVT or pulmonary embolism. In patients with PC deficits warfarin substance has been proved to be the finest treatment for thrombotic accident.

2. Severe Deficit in PC

Recommendations for the initial and continuous treatment of patients with severe PC a lack was released by the International Committee on Thrombosis and Haemostasis. Severe PC deficient infants require prompt initiation of treatment to prevent the condition from rapidly progressing to death. Alternative treatments must be used because heparin administration, inevitably, has little effect on the disease's course. Despite this PC replacement with Factor IX concentrates has been used effectively for long-term management, there has been certain concern as to the treatment's potential to raise the risk of thrombosis. Human vapour-heated PC concentrates, which have been used for many years in Europe, recently became open for controlled use in the U.S [5].

3. Long term treatment

Significant PC deficit treated through the long term for patients with severe PCa, the International Committee on Thrombosis and Haemostasis released standards for both initial and continued treatment. If one wants keep the disorder from rapidly advancing and eventual death, severe PC deficient young children need to start treatment right away. Heparin administration, of course, has minimal effect on the growth of the disease; therefore, alternative treatments must be sought. The use of PC replacement with Factor IX concentrates has been used successfully for continued use some people are worried about how the treatment can increase the risk of thrombosis. Although years of use in Europe, human vapour-heated PC concentrates were recently made legal for regulated use in the USA [6].

2. CASE REPORT

A 21 years male patient came to ER department with the chief complaints of Giddiness, Chest pain, seizures, and 2 episodes of vomiting with elevated blood pressure 200/140 mmhg. He had no past medical history. Patient was initially treated with injection Labetalol 20mg intravenously to control blood pressure. Patient complete blood picture depicted increased WBC Count, Complete Urine analysis revealed mild proteinuria. Serum Electrolytes were normal. For further investigations laboratory tests were advised, which are demonstrated in Table 1. CT scan of Brain showed normal Brain parenchyma, CT Head and Neck showed P1 segment of Right posterior cerebral artery appears hypoplastic. Anterior and Posterior circulation vessels appear normal. Colour Doppler evaluation of carotid and vertebral vessels, USG abdomen, and colour Doppler evaluation of renal arteries were also normal MRI BRAIN revealed Multi Focal Areas restriction on diffusion with flair hypertension noted in left fronto parieto occipital gray white matter subcortical and deep white matter, posterior body of corpus callosum – Acute Infarct as shown in the Figure 1.

Based on the above findings patients were diagnosed with Protein C deficiency with Acute Ischemic Stroke. Acute ischemic stroke (AIS) is a medical emergency that occurs when blood flow to the brain is reduced or blocked, resulting in brain cell damage. Upon diagnosis patient was treated with the medications as mentioned in Table 2.

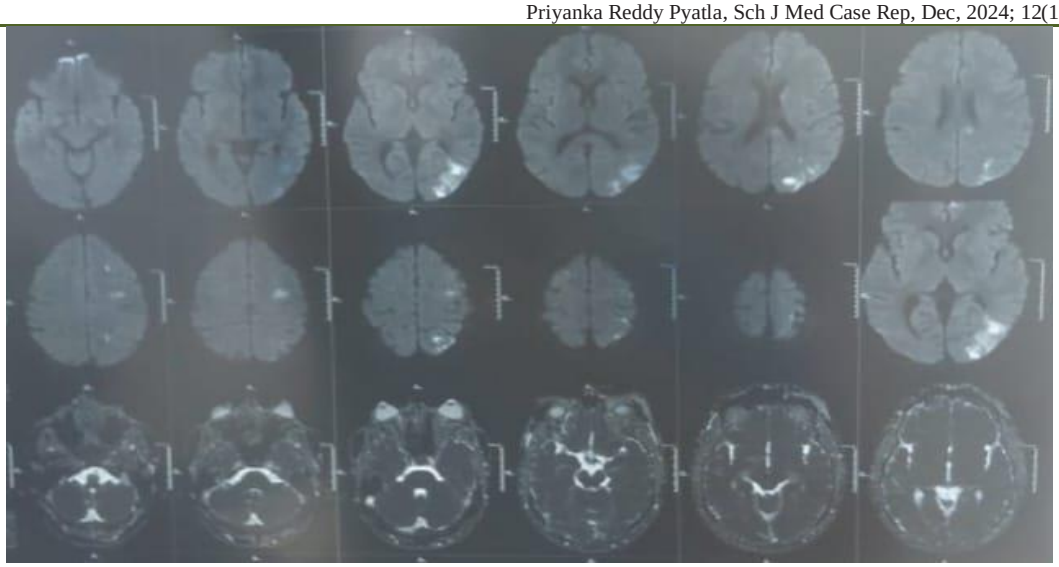

Figure 1: Patients MRI Scan revealing Acute Infarct

Table 1: Laboratory Findings

1. Lipid Profile		**4. Liver Function Tests**	
Parameters	**Value**	**Parameters**	**Value**
T. Cholesterol	194.4 mg/dl	T.Bilirubin	0.71 (<1.2)
HDL Cholesterol	47.3 mg/dl	D.Bilirubin	0.31 (<0.2)
LDL Cholesterol	136.4 mg/dl	Ind. Bilirubin	0.4 (<1)
VLDL	27.96 mg/dl	SGPT	16 (<41)
Serum. Triglycerides	139.8 mg/dl	ALP	93 (40-129)
2. Serum Electrolytes		T.P	5.74 (6-8)
Sr. Sodium	142 mmol/L	Sr. Albumin	3.44 (3.5-5.2)
Sr. Potassium	4.1 mmol/L	Globuin	2.3 (2.5-3.5)
Sr. Chlorine	111 mmol/L	AIG	1.49
Sr Calcium	8.25 mg/dl	GGT	44 (6-42)
3. Protein C Functional Activity (Choromogenic Optical)	**45.90 (83-168)**	ESR	**20mm** (0-10)
		CRP	**29.01mg/L** (<5.0)

Table 2: Treatment Chart

S. NO	DRUGS	GENERIC NAME	DOSE	ROUTE	FREQUENCY
1	INJ.LEVERA	Levetiracetam	1gm	I.V	BD
2	INJ.OPTINEURON	Vit B1, B6	1amp	I.V	OD
3	INJ.STROCIT	Citicholine	500mg	I.V	BD
4	T.CLOPITAB	Clopidogrel	75mg	PO	OD
5	T.ROSUVAS	Rosuvastatin	80mg	PO	OD
6	T.VERTIN	Betahistin	16mg	PO	TID
7	INJ.MANNITOL	Mannitol	20%	I.V	TID
8	T.TELMA	Telmisartan	40mg	PO	OD
9	T.CINOD	Clonidipine, Telmisartan	5mg	PO	OD

Table 3: Discharge Medications

S. NO	DRUGS	GENERIC NAME	DOSE	FREQUENCY
1	Tab Levera	Levetiracetam	1gm	BD
2	Tab Strocit	Citicholine	500 mg	BD
3	Tab Atorvas	Atorvastatin	80mg	OD
4	Tab Vertin	Betahistin	16mg	BD
5	Tab Clopitab-A	Clopidogrel + Aspirin	75mg	OD
6	Tab Clinidipine	Clinidipine	5mg	OD
7	Tab Telma	Telmisartan	40mg	OD
8	Tab Homin-D3	Calcium + Vit D3	1 tab	OD

3. DISCUSSION

A convoluted relationship of hereditary and environmental risk factors contributes to the multi-causative nature of arterial ischemic stroke. The coagulation pathway is linked to the pathophysiological features of arterial ischemic stroke by a number of lines of evidence. It has been proposed that elevated clotting protein levels, including those of factors VIII and XI, are independent risk factors for ischemic stroke. On the other hand, a congenital lack of factors VIII, IX, and XI protects against heart disease and stroke. The risk of ischemic stroke is decreased by anticoagulants. Warfarin is not inferior to aspirin, which is frequently cited as the "standard of practice" for preventing first or recurrent stroke, when it comes to secondary prevention of non-cardioembolic ischemic stroke. When rivaroxaban was added to aspirin, it decreased cardiovascular events, including stroke, in patients with stable atherosclerosis, even though it was not more effective than aspirin at avoiding recurrence following embolic stroke of unknown cause. In hospitalized medically unwell patients, long-term betrixaban medication decreased the risk of later stroke by preventing venous thrombosis. Adults, especially young patients, who have a protein C deficit, have a little but significant increased risk of arterial ischemic stroke [3]. As discussed above this is a peculiar case where young adult has developed ischemic stroke due to genetically predisposition of decreased protein c levels. In such cases early detection and management are necessary for good control of disease.

4. CONCLUSION

PC deficiency is an autosomal disorder that can affect both heterozygous and homozygous persons. The diagnosis of PC requires both qualitative and quantitative losses that take place in a thromboembolic scenario. Since the diagnosis and degree of PC absence have been established, each patient must receive the appropriate therapy and follow-up care. Oral anticoagulation is a component of long-term treatment for PC insufficiency, whether it is homozygous or heterozygous. FFP should be used as a PC replacement therapy until the purpuric lesion has healed before starting the crucial treatment component, coumarone therapy. Heparin should be given concurrently with medication for the first three to six weeks in order to prevent the formation of CISN, albeit this is unlikely in individuals who have PCa deficits. One helpful option is PCC-assisted PC replacement therapy. Because of this, using procoagulants in certain preparations may make the patient's symptoms worse. To avoid issues, PCC and heparin should be used together for 35 days. The high cost of this treatment option is one of its disadvantages.

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