

Combined Deficiency of Protein-C and Protein-S; A case series in a Tertiary Care Hospital, Dhaka, Bangladesh.

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INTRODUCTION

Protein-C and protein-S are vitamin K-dependent glycoproteins, that act as natural anticoagulants. The proteolytic activation of Protein-C by thrombin occurs on the surface of endothelial cells and involves thrombomodulin and endothelial Protein-C receptor.

In the presence of Protein-S, phospholipids and calcium, activated Protein-C (APC) inactivates membrane bound factors V (F-Va) and F-VIII-a by their cleavage at the specific arginine residues.

INTRODUCTION: CONTINUE...

Protein-C and Protein-S deficiencies are inherited as autosomal dominant disorders associated with recurrent venous thromboembolism (VTE) and, in most cases, derived from heterozygous missense mutations 78% and 63% respectively¹.

1. Med ACE. EDITor IAL [Internet]. Edu.pl. [cited 2024 Feb 28]. Available from: <https://advances.umw.edu.pl/pdf/2013/22/4/459.pdf>

CASE PRESENTATION

We reported four cases of Combined deficiency of Protein-C and Protein-S in our hospital in last one and half years.

CASE PRESENTATION: CASE-01

Case-01 was a 16 years old boy presented with the complaints of dyspnea and painful swelling of the right leg.

On general examination, he was mildly anemic, heart rate 115 beats/minute and respiratory rate was 22 breaths/minute.

Respiratory-system examination-revealed features of pleural effusion on left lung.

On examination of right lower limb revealed entire right lower limb was swollen but more marked on calf muscle[>35cm from tibial tuberosity], erythema, tenderness, raised temperature and pitting edema were present.

INVESTIGATION FINDINGS: CASE-01:

Complete Blood Count:

Name	Result
Hemoglobin	10.7 gm/dl
ESR	54mm in 1 st hour
WBC	12000/cumm
Neutrophils	72%
Platelet	4400000/cumm

Test Name	Result
Serum creatinine	0.7 mg/dl
Random Plasma Sugar	5.5 mmol/L
Serum procalcitonin	<0.5
D-dimer	>10 mg/dl

- CXR=Mild pleural effusion[L]
- ECG: **Sinus tachycardia**
- Echocardiography: Normal
- Duplex study of right lower limb=Acute deep vein thrombosis involving right ilio-femoro-popliteal venous segment with no sign of recanalization. Arterial system was normal



CASE PRESENTATION:CASE-01

- Wells score² in this patient was 4.

Clinical features of patient	Well's score
Entire right lower limb swollen	1
Localized tenderness along distribution of deep venous system	1
Pitting oedema in right lower limb	1
Right calf muscles swelling was 5 cm larger than left side (Rt-35cm ,left-30 cm).	1

- To exclude any Deep vein thrombosis and Pulmonary Embolism ,we did Modified Wells scoring³ in this patient and the score was 8.5

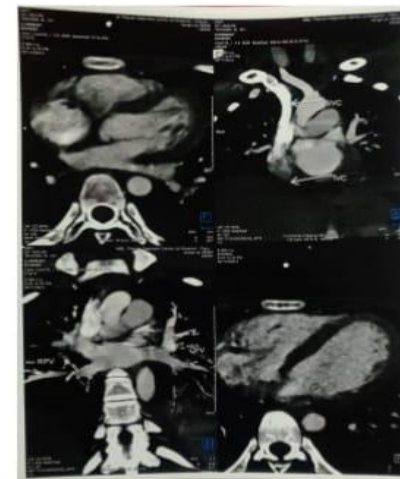
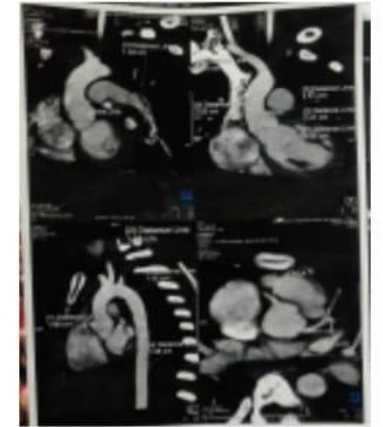
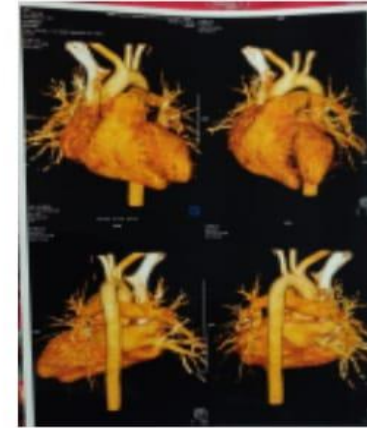
Clinical features of patient	Well's score
Clinical signs and symptoms of DVT in right lower limb	3
No alternative diagnosis	3
HR-115 b/m	1.5
Haemoptysis	1

CASE PRESENTATION:CASE-01

CT Angiogram of pulmonary vessel

- Small eccentric thrombus at left pulmonary artery
- Dilated Main pulmonary artery(MPA: 22.3)
- Mild Pneumonic consolidation involving lateral basal segment of left lower lobe.
- Left sided mild pleural effusion.

CTPA



CASE PRESENTATION:CASE-01

As the patient was very young , so we did Thrombophilia Screening and the test result revealed combined deficiency of Protein-C and Protein-S.

Test Name	Result	Reference Value
Protein-C	26.8%	70-130%
Protein-S	64.3%	60-130%

CASE PRESENTATION:CASE-02

Case-02 was an 18 years old young married girl presented with hematemesis and melaena.

On general examination, she was severely anemic, heart rate was 120 beats/minute.

On abdominal examination, spleen was palpable, firm in consistency and margin was regular.

CASE-02: ON INVESTIGATIONS

Complete Blood Count:

Hemoglobin	4.7 gm/dl
WBC	2000/cumm
Neutrophil	71%
ESR	10 mm in 1 st hour
Platelet	70000/cumm
Reticulocyte count	1.47% [ref <2.5%]
PBF	Microcytic hypochromic anemia

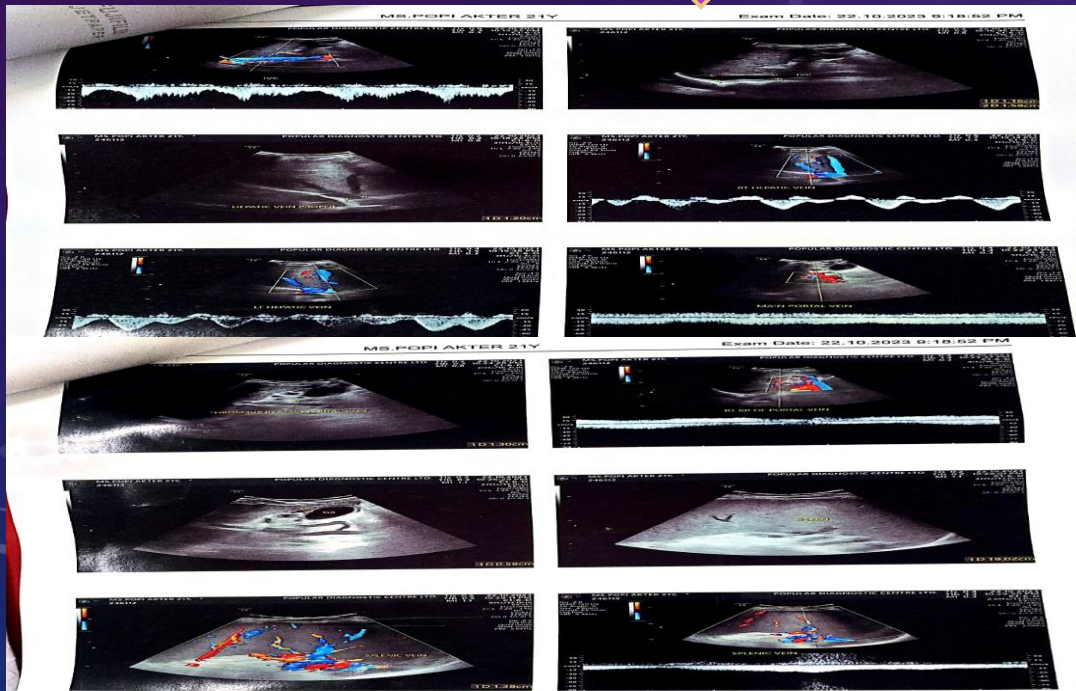
Iron Profile:

TIBC	310 microgram/dl [ref 250-425]
Iron	14 microgram/dl [ref 50-170]
Ferritin	20 ng/d l[ref 10-120]

Test Name	Result	Unit
S. creatinine	0.7	mg/dl
Random plasma glucose	5.5	mmol/L
ALT	40	IU/L
AST	39	IU/L
ALP	35	IU/L
PT-INR	0.91	Ref.<1
HBsAg	Negative	
Anti-HCV	Negative	
S. Albumin	3.8	gm/dl
S. Procalcitonin	<0.5	
D-dimer	2.9	gm/dl

CASE-02: ON INVESTIGATIONS

- USG of whole abdomen: Gross splenomegaly with engorged splenic-hilar vessels.
- Duplex study of portal vein: Portal vein thrombosis with gross splenomegaly and dilated-splenic vein.



- Upper GI endoscopy=Fundal varix



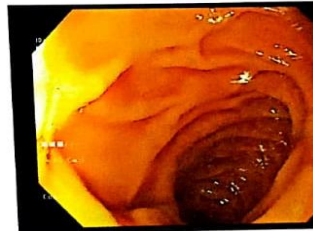
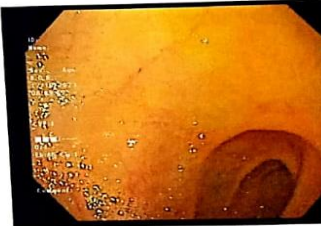
Procedure : VIDEO ENDOSCOPY OF UPPER GIT

Indication : Haematemesis.

Medication : Xylocaine Spray 10%,Jasocaine Jelly.

FINDINGS :

- Oesophagus:- Normal,no varix seen.
- Stomach:- Fundus shows large grape like fundal varices. Rest of stomach appear normal.
- Duodenum:- The bulb, post-bulbar area upto second part appear normal.
- Biopsy:- Not taken.
- COMMENTS : Fundal varix.
- ADV-Cyanoacrylate glue injection.



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CASE PRESENTATION: CASE-02

As the part of cause evaluation, we did Thrombophilia Screening and the result revealed combined deficiency of Protein-C and Protein-S.

Test Name	Result	Reference Value
Protein-C	52%	70-130%
Protein-S	35%	60-130%

CASE PRESENTATION: CASE-03

Case-03 was a 29 years old married young male presented with altered level of consciousness, headache and left sided hemiparesis.

On general examination, heart rate was 78 beats/minute, regular.

On neurological examination, left sided hemiparesis was found.

No cranial nerve deficit was present.

All other systemic examination revealed no abnormalities.

CASE-03: ON INVESTIGATIONS

COMPLETE BLOOD COUNT:

Hemoglobin	16.6 gm/dl
WBC	13000/cumm
Neutrophil	66%
Platelet	410000/cumm
ESR	10mm in 1st hour

SERUM ELECTROLYTES:

Na+	140 mEq/L
K+	4.1 mEq/L
Cl-	101 mEq/L
HCO3-	22 mEq/L

FASTING LIPID PROFILE:

S. Cholesterol	146 mg/dl [ref 150-220]
S. Triglyceride	104 mg/dl [ref <150]
S.HDL	35 mg/dl [ref 35-65]
S.LDL	124 mg/dl [ref <150]

Test name	Result	Unit
Serum creatinine	0.7	mg/dl
Procalcitonin	<0.5	
D-dimer	<0.5	mg/dl
ALT	45	IU/L
AST	35	IU/L
ALP	50	IU/L
VDRL	Non-reactive	
TPHA	Negative	
ANA	Negative	
TSH	0.96 [ref 0.4-5.5]	micro-IU/L
FT4	17.21 [ref 11.5-23.8]	pico-mmol/L

CASE-03: ON INVESTIGATIONS

MRI Of Brain:

Multiple small infarcts in right basal ganglia, paraventricular and sub-cortical location of Fronto-parietal lobes with right CP angle arachnoid cyst.



ECG: Within normal limit

Echocardiogram: Normal

MRI of Brain

Technique: T1WI Sagittal, T2WI coronal & T1WI, T2WI, FLAIR and DWI axial.

Clinical H/O: LSH, headache and vertigo.

FINDINGS

- Multiple small diffusion restricted areas are noted at right basal ganglia, paraventricular and subcortical location fronto-parietal lobes which appear hyperintense on T2 and FLAIR & hypointense on T1WI.
- Small extra axial CSF intensity lesion in all sequence noted at right CP angle.
- No mass effect or midline shift is evident.
- Ventricles and extra ventricular CSF space are unremarkable.
- Sellar and para sellar regions appear normal.
- Pituitary gland is normal.
- The posterior fossa, brain stem & left CP angle appear normal.
- Visualized parts of cranial nerves appear normal.
- Mucosal thickenings are seen in both maxillary, ethmoid and sphenoid sinuses – sinusitis.

IMPRESSION: MRI features suggest –

- Multiple small acute infarcts in right basal ganglia, paraventricular and subcortical location fronto-parietal lobes.
- Right CP angle arachnoid cyst.

CASE PRESENTATION: CASE-03

As this patient presented with Acute Ischemic Stroke at very young age, so we also did Thrombophilia Screening and the result showed Combined deficiency of Protein-C and Protein-S.

Test Name	Result	Reference Value
Protein-C	63%	70-130%
Protein-S	53.7%	60-130%

CASE PRESENTATION: CASE-04

Case-04 was a 61 years old hypertensive woman admitted with right upper limb ischemia due to thrombosis of right ulnar artery.

On general examination, she had tachycardia[Heart rate 116 beats/min] and tachypnea[Respiratory rate 22 breaths/min].

Respiratory-system examination-revealed features of left sided consolidation.

Examination of right upper limb revealed entire limb was swollen but more marked on below elbow joint. Tenderness, raised temperature and pitting edema were present along with erythema and blackening.

CASE-04: ON INVESTIGATIONS

Complete Blood Count:

Hemoglobin	13.3 gm/dl
WBC	10700/cumm
ESR	27 in 1 st hour
Platelet	211000/cumm

Serum Electrolytes:

Na+	137 mmol/L
K+	4.2 mmol/L
Cl-	105 mmol/L
HCO3-	24 mmol/L

Fasting Lipid Profile

S. Cholesterol	184 mg/dl [ref <200]
S. Triglyceride	233 mg/dl [ref<200]
HDL	45 mg/dl [>35]
LDL	116 mg/dl [ref <130]

Test Name	Result	Unit
S. Creatinine	1.2	mg/dl
RPG	7.0	mmol/L
ANA	Negative	
S. Procalcitonin	<0.5	mg/dl
D-dimer	<0.5	mg/dl
Sputum for gene-X-pert	Negative	
TSH	0.56[ref 0.4-5.5]	micro-IU/L
FT4	18.21 [ref 11.5-23.8]	pico-mmol/L

CASE-04: ON INVESTIGATIONS

- **ECG: Features of LVH**
- **Echocardiogram:**
Concentric LVH with good LV systolic function.
- **Chest X-ray P/A View: Left sided middle zone consolidation and Mild Cardiomegaly**

Duplex study of right upper limb:

- Thrombotic occlusion of right ulnar artery.
- Venous systems are normal.

CASE PRESENTATION: CASE-04

As this patient presented with features of recurrent Right Upper Limb Ischemia due to right ulnar artery thrombosis, So we performed Thrombophilia Screening Test and the result also showed combined deficiency of Protein-C and Protein-S.

Test Name	Result	Reference Value
Protein-C	73.1%	70-130%
Protein-S	51.3%	60-130%

THE DIAGNOSES

Heading	Case-01	Case-02	Case-03	Case-04
Diagnosis	Acute pulmonary embolism due to DVT of right lower limb due to combined deficiency of protein-C and protein-S	Portal vein thrombosis with fundal varix[non-cirrhotic] due to combined deficiency of protein-C and protein-S.	Ischemic stroke with left sided hemiparesis due to combined deficiency of protein-C and protein-S.	HTN with Right upper limb ischemia due to thrombosis of right ulnar artery due to combined deficiency of protein-C and protein-S with CAP

- After proper diagnosis , all of the four patients received specific and general management according their clinical conditions.
- The ultimate outcomes were excellent without any complications.
- Further follow-up of the respective patients was also done.

CONCLUSION

As protein-C and protein-S deficiency are rare inherited disorders [autosomal dominant], young patients with features of DVT should be considered as Protein-C Protein-S disorders and must be treated with the most efficient treatment options available as soon as possible for better outcome and patient compliance.

