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CASE REPORT: NEONATAL THROMBOSIS

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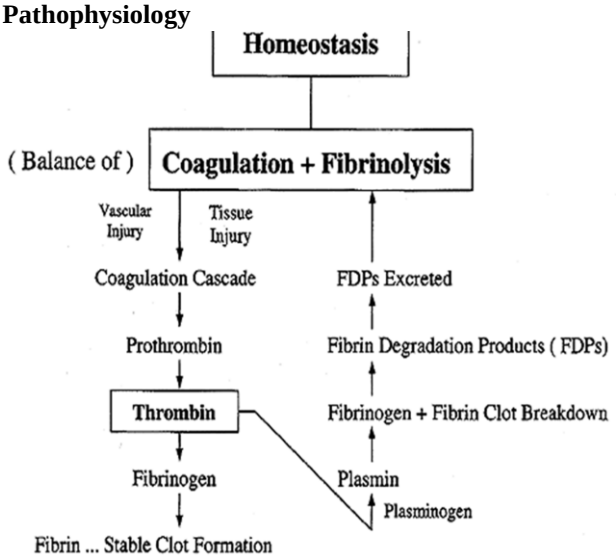
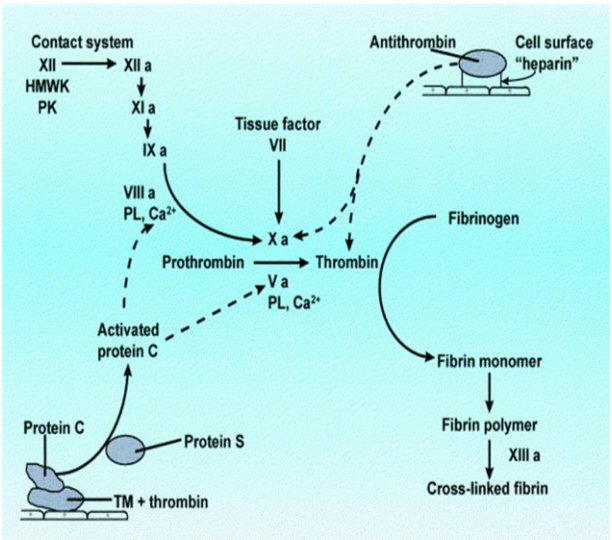
Protein C deficiency is a congenital or acquired condition that leads to increased risk for thrombosis.

Congenital protein C deficiency is one of several inherited thrombophilia, which are a heterogeneous group of genetic disorders associated with an elevated risk of venous thromboembolism.

Pathophysiology





Protein C System - 3 abnormalities
Protein C deficiency, Protein S deficiency, Mutation of factor V cleavage site (activated protein C resistance).

Hereditary Protein C deficiency:- Autosomal Dominant most patients heterozygous, rare severe homozygous - purpura fulminant. Activity levels 50% of normal, and there is increased risk of venous thrombosis.

APC Resistance - Mutant Factor V (Factor V Leiden):- Activated Protein C (APC) destroys factor Va by cleaving it at arginine 506.Some patients have a mutated factor V with a glutamine at position 506, this prevents APC from cleaving factor Va and destroying it.Defect is termed Factor V Leiden or APC resistance. Increased risk of venous thrombosis.

Epidemiology
In the United States and worldwide, protein C deficiency by plasma level alone is found in 1 in 200 to 1 in 500 persons in the general population.

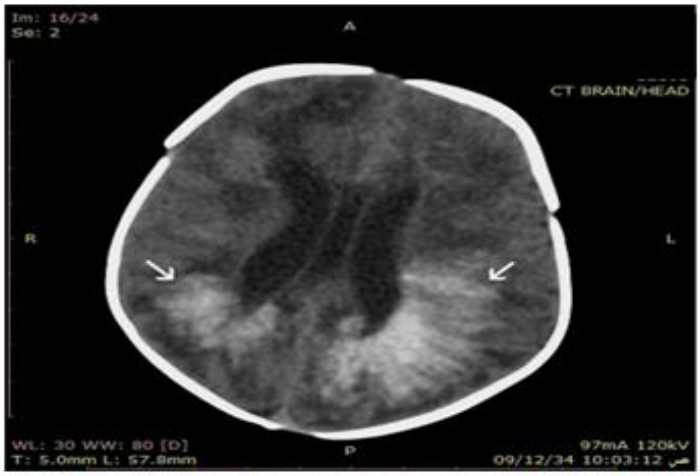
Severe homozygous or compound heterozygous protein C deficiency occurs in approximately 1 in 500,000 to 1 in 750,000 live births.

Clinical Presentation
Physical: - Patients with symptomatic hereditary protein C deficiency may present with VTE or WISN Homozygotes and compound heterozygotes frequently present with NPF during the first hours of life.

Venous thromboembolism
Deep venous thrombosis of the lower extremity a chronic condition associated with swelling, pain, discoloration, and venous insufficiency of the lower extremity.

Neonatal purpura fulminans
Affected neonates present with diffuse ecchymosis which, similar to the lesions of WISN, progress to form necrotic bullae if appropriate therapy is not rapidly instituted.

May be presented by intracranial Hge



Unenhanced axial brain CT scan shows bilateral cortical and subcortical hyperattenuating lesions indicating haemorrhage (arrows).

May present with bilateral adrenal hemorrhage

Differential Diagnosis of congenital and acquired hypercoagulopaty

Acquired	Congenital
Antiphospholipid antibody syndrome	Protein C deficiency
Malignancy	Protein S deficiency
Surgery / Trauma	Antithrombin Ⅲ deficiency
Liver disease	Factor V Leiden
Vit K deficiency	Prothrombin gene G20210A mutation
DIC	Hyper-homocysteinemia
Severe sepsis specially Gm –ve	Dysfibrinolysis

CASE PRESENTATION

Full term male – 2.5 kg – to G6P4+1 uneventful pregnancy , product of C.S in Al-Ahli Al Saudi hosp. because of bad CTG and fetal distress MSAF, delivered sleepy required only tactile stimulation then picked up.

A/S :- 5/1min 85min / Admitted in NICU and kept in NPO, IVF, IV antibiotic All investigation were within normal Bl. gas normal – CXR clear lung field. On 2nd day of life developed convulsion in form of blinking of eyes , frothy oral secretion , with desaturation so loaded by phenytoin , baby was stable maintain saturation on oxyhood 3L/min.

They sent fax to MCH for further investigation and anti-convulsion therapy.

Differential diagnosis

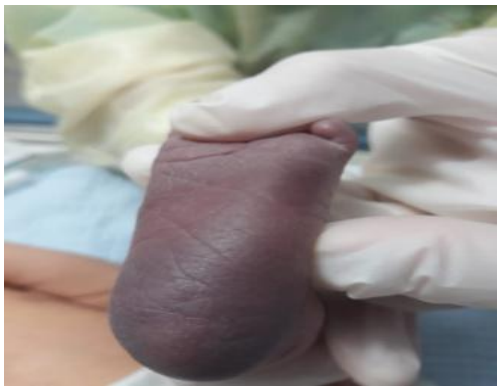
- Hypoxic ischemic encephalopathy
- Transient metabolic disturbances
- Focal ischemic injury (arterial infarction – venous infarction) Intra cranial Hge
- Infection (congenital infection, meningitis, septicemia)
- Inborn error of metabolism (pyridoxine dependency, glycine encephalopathy, maple syrup urine disease)
- Brain anomaly
- Epileptic syndromes (benign familial neonatal seizures, benign idiopathic neonatal seizures)
- Maternal drug withdrawal
- Kernicterus.

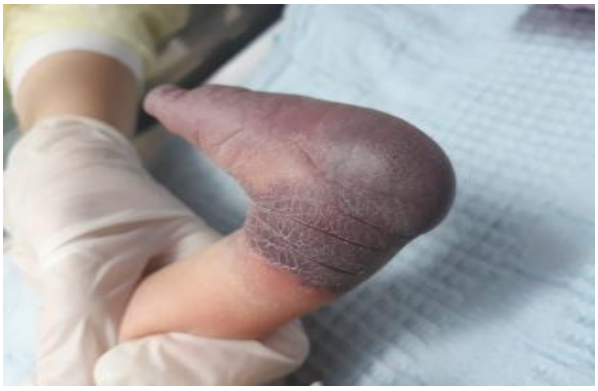
On 3rd day of life baby came to ER after discharge from the other hospital. Baby was admitted as a case of neonatal seizure with fever for investigation full sepsis work up done started amika-vanco CT was requested to be done in the morning.

On 4th day of life

- LP: - WBC 1320 poly 57.3% mono 42.7%, Glucose 0.5 Protein 183 RBCs 5000
- (D/C amika, start cefotaxime)
- CBC and chemistry were acceptable

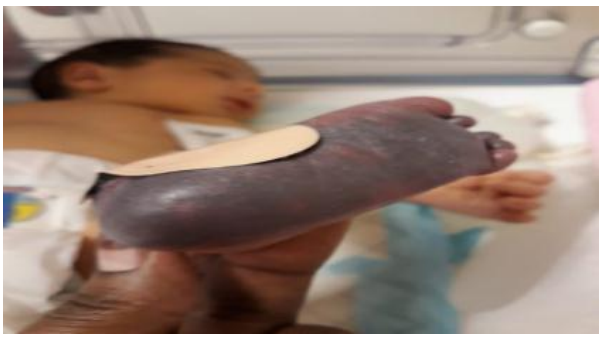
- Brain ultrasound was done in the morning: - showed large left cerebral parenchymal Hge with normal size lat. ventricle and no midline shift
- CT was done: - multi- focal left hemispheric acute cerebral Hge and a focal hypo-attenuating area in left aspect of the brain stem for clinical correlation.





1- Urgent Doppler ultrasound:- Normal wave of DPA, PTA and popliteal artery.
2- Surgical consultation:- Start hot compresses – line of demarcation to be observed - no surgical intervention indicated.
3- Vascular consultation:- Left foot area red and blue – no definite history of canulation or pricking – discoloration of the whole foot – triphasic Doppler signals of DPA and PTA left side swelling of left foot? Compartment S – recommendation baby has good vascularity of left foot limb elevation – no vascular surgery intervention.
4- Hematology consultation:- conservative management like warm fomentation and put nitroglycerine.

Cefotaxime was D/C and started meropenam, ID consultation done they ordered for meropenam 10 days and vanco for 5 days.



A discussion between our COD and hematology consultant resulted in to give FFP after taking sample for protein C, S and factor XIII.

On the next 2 days there was some sort of improvement in the color of the foot and there was no need to sta start heparin.

On the 7th day baby was irritable and in pain full examination was done and there was Lt Testis swelling, hard painful in touch.

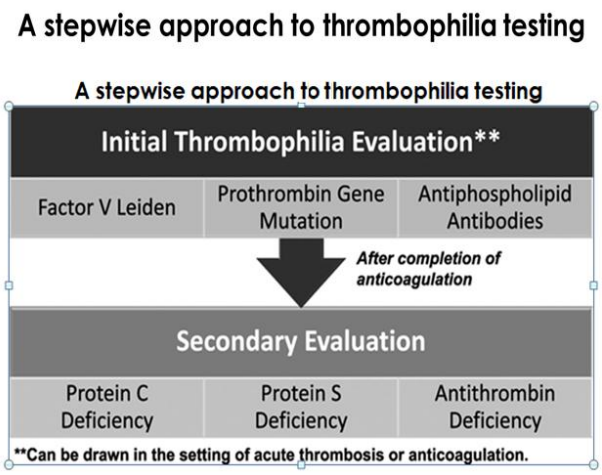
- Urgent Doppler ultrasound done showed Rt. testis normal size, echogenicity and blood supply.
- While Lt Testis enlarged in size 9x9 mm mixed echogenicity with only venous Bl. supply.
- No arterial vascularity detected, suggesting testicular torsion.
- Urgent pedia-surgery consultation was done and baby went to OR.
- There was no torsion.
- Gangrenous Lt testis, part of it sluphed during manipulation and sent to histopathology.
- Immature testicular tissue with hemorrhagic infarction mostly thrombosis.

On the 10th day factor V Leiden, VIII, homocysteine level CT angio was requested showed Lt intra-cerebral hemorrhagic infarction with normal cerebral vein and sinuses no sign of venous thrombosis seen

- Factor XIII was within normal levels
- Anti-thrombin III was within normal levels
- Factor V leiden was within normal levels
- Factor VIII was within normal levels
- Homocysteine level was within normal levels
- Protein S activity was normal 67%
- Protein C activity was 6% (normal 70-130)
- Baby was discharged at 19 day old, hemodynamic stable to follow up.

In fact, testing for an inherited hypercoagulable state is costly & likely to uncover an abnormality in more than 60% of patients presenting with idiopathic VTEs.

Although, the remaining 40% will have unremarkable test results, this does not imply a true absence of a hypercoagulable state.



Workup
A variety of immunologic and functional protein C assays are available.

Immunologic assays
Immunologic methods for the measurement of protein C antigen include enzyme-linked immunosorbent assays (ELISAs), radioimmunoassays (RIAs), and electroimmunoassays.

Functional assays
Activated protein C (aPC) activity can be measured by means of a clotting assay or a chromogenic substrate. The adult reference range for protein C activity tends to be slightly lower than the immunologic normal range

Screening
The timing of testing with respect to acute thrombosis and warfarin therapy deserves special mention.

Acute thrombosis
The levels of protein C, protein S, and antithrombin are reduced in the setting of acute thrombosis. Therefore, these levels should generally not be assessed at the time of presentation with acute VTE. However, a normal protein C activity in this setting essentially rules out hereditary protein C deficiency.

Warfarin
Because protein C is a vitamin K–dependent protein, its levels are reduced with warfarin administration.

Therefore, it is recommended that protein C testing not be performed unless the patient has been off vitamin K antagonist therapy for at least 2 weeks. If the patient has a severe thrombotic diathesis that does not permit discontinuation of anticoagulation.

Treatment
A substantial proportion of individuals with protein C deficiency remain asymptomatic throughout life and require no specific therapy.

However, thromboprophylaxis may be considered in such individuals, particularly if there is a strong family history of thrombosis.

A case report by Milleret and colleagues describes 2 years of successful prophylaxis in a patient with neonatal severe protein C deficiency, using warfarin oral suspension. The international normalized ratio (INR) was measured by home monitoring, with a target INR of 2.5 to 3.5.

For those patients who do develop clinical manifestations of hereditary protein C deficiency, treatment depends on the particular clinical syndrome: venous thromboembolism (VTE), warfarin-induced skin necrosis (WISN), or neonatal purpura fulminans (NPF).

Venous thromboembolism
VTE in patients with protein C deficiency is managed in much the same way as it is for patients with VTE due to other causes.

Because the risk of recurrent VTE in protein C –deficient patients may be as high as 60%, long-term anticoagulation is often recommended, particularly following a spontaneous thromboembolic event.

Warfarin-induced skin necrosis
WISN is a medical emergency that requires treatment as soon as it is recognized.

Therapy consists of immediate discontinuation of warfarin, administration of vitamin K, and initiation of therapeutic doses of heparin.

If the patient is protein C deficient, exogenous protein C should be administered, either in the form of fresh frozen plasma (FFP) or, preferably, as purified protein C concentrate (Ceprotin).

Neonatal purpura fulminans
Like WISN, NPF is a medical emergency that requires rapid normalization of plasma protein C activity. Although fresh frozen plasma has been used as a source of exogenous protein C in the treatment of NPF, frequent administration is required to maintain adequate plasma levels, thereby limiting its usefulness in this setting.

Highly purified protein C concentrate (Ceprotin) represents an attractive alternative that does not subject patients to the high volume and protein load of fresh frozen plasma.

After treatment of the acute phase of NPF, patients are transitioned to anticoagulation therapy, on which they must remain indefinitely. Warfarin may be used in this setting, provided that exogenous protein C is administered during its initiation in order to avoid the development of WISN. For patients with breakthrough thrombosis despite anticoagulation.

Living donor liver transplantations have been successfully performed in NPF, resulting in a permanent cure

- Heparin
- Enoxaparin (Lovenox)
- Dalteparin (Fragmin)
- Warfarin
- Protein C concentrate (Ceprotin)
- Fresh frozen plasma

Medication

Ceprotin®

Ceprotin® is a highly purified plasma-derived concentrate of human protein C zymogen.

Early case reports on the treatment of newborns with severe protein C deficiency and neonatal purpura fulminans demonstrated an impressive response to substitution therapy with protein C concentrates.

Protexel®

Protexel® (LFB, Les Ulis, France) is a protein C zymogen concentrate, derived from human plasma (Radosevich et al 2003).

Drotrecogin alpha activated (Xigris(®)

Drotrecogin alpha (activated) (Xigris®, Eli Lilly Co.) is available as is a recombinant analogue to the physiologic human activated protein C.

A report was published by a Japanese group, who used another concentrate of activated protein C to treat a female newborn who developed purpura fulminans on the third day after birth due to homozygous protein C deficiency (Nakayama et al 2000).

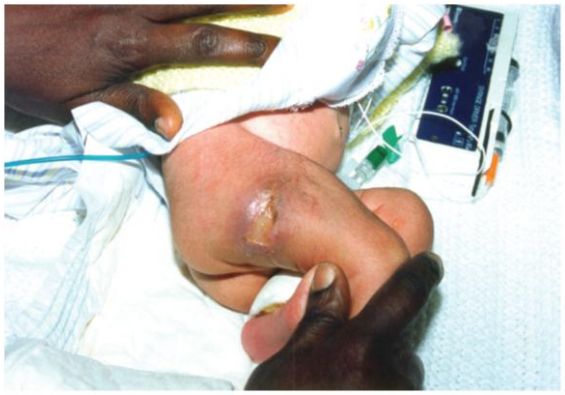


Figure 1b The same child 6 days after beginning of protein C replacement with Ceprotin®.