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Paroxysmal nocturnal hemoglobinuria presenting as cerebral venous sinus thrombosis: a case report

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Abstract
Paroxysmal nocturnal hemoglobinuria (PNH) is an acquired hemolytic anaemia characterized by a triad of intravascular hemolysis, pancytopenia and tendency for venous thrombosis. Patients with PNH present with these features which occur in various combinations as described in this case report. Several episodes of intravascular hemolysis result in hemoglobinuria associated with thrombosis at unusual sites and these patients may have varying degree of bone marrow disorders. Diagnosis can be confirmed by flow cytometry of blood granulocytes and FLAER assays. Management was supportive with transfusion and treatment of thrombosis in the past. But in the recent years the evolution of treatment strategies like hemopoietic stem cell transplantation and complement inhibition with eculizumab though very costly have been shown to be very effective.
Cerebral venous system is the second most frequent location of thrombosis after hepatic veins. However, data about PNH related cerebral venous thrombosis (CVT) are very scarce because of the rarity of both the disorders. Here we report a 35y old woman who presented with altered sensorium, with a history of headache. On evaluation, we found there was anemia with evidence for hemolytic anemia and cerebral venous thrombosis. With these clinical features, we suspected paroxysmal nocturnal hemoglobinuria which was later confirmed by flow cytometry.

Keywords: *PNH (Paroxysmal nocturnal hemoglobinuria), Hemolytic anaemia, Cerebral venous thrombosis (CVT), Flow cytometry, Eculizumab*

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I. Introduction

PNH is a rare acquired clonal hematopoietic stem cell disorder characterized by abnormal sensitivity of red blood cells to lysis by complement. It is caused by genetic mutation resulting in deficiency of glycosyl phosphatidylinositol anchor (GPA) for cell membrane proteins including complement regulating proteins CD55 and CD59[1]. Available reports suggest that the incidence of clinically significant disease is in the range of 1 to 10 cases per million population and it is chiefly a disease of adults and the peak age of onset is in thirties[2]. It is considered unique condition in a sense that its manifestations may include hemolytic anemia (due to acquired intracorpuscular defect), pancytopenia (due to marrow failure) and tendency to have venous thrombosis[2]. Hemolysis occurs throughout the day but patients may present for passing red concentrated urine in the morning. As urine is more concentrated in the morning, this is when colour is more pronounced. The hypothesis of increased hemolysis at night during sleep due to acidosis or low steroid levels is not supported by studies. The gold standard diagnostic test for PNH is flow cytometry of RBCs to demonstrate absent or reduced expression of both CD55 and CD59[3]. Patients with PNH experience a high incidence (14-40%) of thrombotic events, mostly venous and rarely arterial[4]. Thrombotic events in PNH may occur despite thrombocytopenia or pancytopenia and they have a predilection for unusaual locations in the venous system. The vessels mostly involved are visceral veins (hepatic, portal, mesenteric, splenic, and renal veins), followed by cerebral and dermal veins. Here we report a case of young female who had history of these combination of symptoms and signs that made us to diagnose this rare disorder.

II. Case History

A 35 year old married woman came with altered sensorium, severe frontal headache with blurring of vision and vomiting for one day. She was admitted in an outside hospital 2 year prior with episode of abdominal pain and anemia for which blood transfusion was done with further work up. There was no history of trauma/fever or illicit drug abuse. Her menstrual cycles were regular and she had normal vaginal delivery with

one living healthy child. On examination she was hemodynamically stable and moderately anemic. Neurological examination revealed Glasgow Coma Scale (GCS) 12/15, normal power, extensor right plantar response and bilateral papilledema on fundoscopic examination. Spleen and liver were not palpable on abdominal examination and rest of the examination was unremarkable.

Laboratory investigations showed hemoglobin of 6.6 g/dl with MCV 96 fl, reticulocyte count 2.2% (corrected 1%) and normal platelet and total leucocyte count. Iron profile suggestive of Iron deficiency anemia with S. Iron 23ug/dl, TIBC-502ug/dl, S.Ferritin 1.7ng/ml.

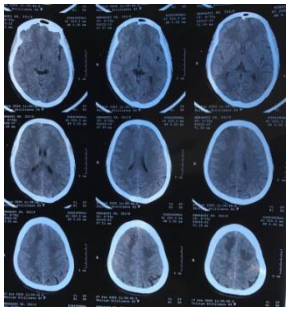

Figure 1

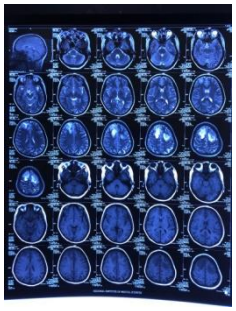

Figure 2

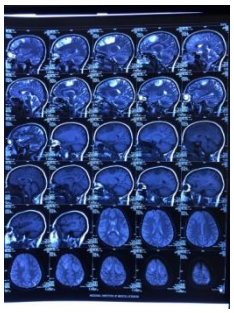

Figure 3

S.Vit.B12, folate levels were normal. Liver function and Renal function tests were normal. Lactate Dehydrogenase (LDH) came out to be markedly increased (1167 mg/dl). Urine routines were normal. Ultrasound abdomen including kidneys and urinary bladder were normal. With above parameters we thought about hemolytic anemia and Workup for connective tissue diseases like ANA and dS-DNA done and found to be negative. Bone marrow biopsy was done and revealed hypercellular marrow with no other abnormality. Blood and urine cultures were sterile. Fever profile including malaria, typhoid, scrub, dengue, Japanese encephalitis was negative.

Computerized Tomography (CT) of brain scan was done on the day of admission that showed a hypodense lesion in bilateral frontal region, intra-cerebral hemorrhage and hemorrhagic infarct (Figure 1). Meanwhile patient developed generalized tonic-colonic seizures. He was managed accordingly with antiepileptic and analgesic drugs. Magnetic Resonance Imaging (MRI) of brain including Magnetic Resonance Venography (MRV) was performed. Radiological signs confirmed the diagnosis of superior sagittal sinus thrombosis (Figure 2&3). Patient was started with anticoagulation therapy along with other supportive measures and her condition improved gradually. Since thrombosis was made out we worked her up for thrombotic states. Homocysteine level was normal. Coagulation profile was normal. The hematological tests sent earlier showed negative Coombs' test and both Glucose 6 Phosphate Dehydrogenase (G6PD) levels and hemoglobin electrophoresis were normal. Later ophthalmologist suspected branched retinal vein occlusion and advised fluorescein angiogram but patient was not willing for the procedure.

Our patient had hemolysis as evidenced by raised LDH, thrombosis at multiple sites (Cerebral venous sinuses and possibly retinal vein) and anemia. This triad of features made us to suspect PNH. Screening with Hams test turned out to be positive. In order to confirm the same, we did flow cytometry which showed evidence of PNH clone upon analysis of granulocytes and monocytes [CD59-41% NEG (>20% NEG in granulocytes) and CD 55– 46.7% NEG].

With the classical triad of features and a positive flow cytometry final diagnosis of paroxysmal nocturnal hemoglobinuria was made. Hematologist opinion was sought. Patient was started on heparin and overlapped with warfarin and discharged with warfarin when International Normalized Ratio (INR) was achieved with target range. She was also given two units of packed cell transfusion. She was also started with steroids and iron, folic acid supplementation and is currently on outpatient follow up. Eculizumab could not be used because of its non availability and unaffordability by the patient.

III. Discussion

In PNH there is complement induced lysis of RBCs due to the abnormal sensitivity of RBC cell membrane. This is due to an acquired defect in the gene for phosphatidylinositol class A (PIGA) thereby causing deficiency of glycosylphosphatidylinositol (GPI) which is sheet anchor for cell membrane proteins[3]. CD55 and CD59, complement regulatory proteins which block intravascular and extravascular hemolysis respectively in normal human, are deficient in PNH[4]. Hemolysis occurs in PNH because these patient's RBC's lack GPI anchor which is required to attach CD55 and CD59 to the surface of RBC[4]. This permits unregulated

formation of certain complement attack complex which damages RBC membrane resulting in intravascular hemolysis. This causes reduction in hemoglobin and hemoglobinuria with resultant increase in LDH[3].

Next feature is thrombosis which is the leading cause of death in patients with PNH[4]. The pathogenesis causing thrombosis is not completely understood; but hypothesized to be due to free hemoglobin resulting from hemolysis attracts nitric oxide which induces vasoconstriction and damages the vascular endothelium forming a nidus for thrombus formation. Also platelets release procoagulant particles during complement induced hemolysis, which facilitate thrombosis. Thromboses involve the venous rather than the arterial system[4].Venous thrombosis often occurs in locations such as hepatic, portal, mesenteric, dermal, and cerebral veins[5]. Minority of patients develop pancytopenia due to bone marrow disorders like aplastic anemia or primary myelofibrosis.

Cerebral venous sinus thrombosis (CVT) in PNH usually involves superior sagittal sinus producing edematous, congested cortex and a tendency for hemorrhagic infarction. It clinically presents with signs and symptoms of raised intracranial pressure (headache, vomiting and papilledema). The gold standard diagnostic test for CVT is MR venography. The treatment options for hemolytic anemia in PNH include blood transfusions, pulse steroids for acute attacks, folic acid, iron supplements, low dose prednisolone and eculizumab (humanized monoclonal antibody against complement C5) for chronic hemolysis. Iron replacement can stimulate reticulocytosis that can trigger hemolysis by releasing new cohort of complement sensitive cells. This can be prevented by adding prednisone during replacement therapy.

Intravascular hemolysis is the dominant feature of classic PNH, and this process is blocked by the complement inhibitor eculizumab with decreased need of blood transfusions and marked improvement in signs and symptoms and quality of life [6,7]. The thrombotic tendency of PNH also appears to be ameliorated by eculizumab. The 5 year survival of patients with PNH prior to eculizumab therapy was 67% and has improved to 96% in patients who used the monoclonal antibody. The medication also decreased the risk for thrombotic events from 6% per year to less than 1% per year. It has been shown that eculizumab therapy, which is effective in decreasing hemolysis, can also decrease the risk for venous thrombosis [8,9].

IV. Conclusion

PNH-related CVT are rare, with no specific characteristics except for a marked preponderance in young females, a frequent association with past or concomitant abdominal vein thrombosis, and a more complex initial therapeutic approach, requiring a close collaboration between neurologists and hematologists. In this presentation, a young girl who presented to us with anaemia and hemorrhagic cerebral infarct with history of abdominal pain was found to have coomb's negative hemolytic anemia and cerebral venous thrombosis. It has always been said that in a case of confusing cases of hemolytic anaemia and pancytopenia, we must suspect paroxysmal nocturnal hemoglobinuria (PNH); more so when it is coupled with venous thrombosis. Having diagnosed PNH, A spontaneous long-term remission can occur, which must be taken into account when considering potentially dangerous treatments, such as bone marrow transplantation. Platelet transfusions should be given, as appropriate, and long-term anticoagulation therapy should be considered for all patients. The recommended management is very costly and affordability for the patient is debated.[8,10]

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