Journal Homepage: - www.journalijar.com
INTERNATIONAL JOURNAL OF ADVANCED RESEARCH (IJAR)
Article DOI: 10.21474/IJAR01/6115
DOI URL: http://dx.doi.org/10.21474/IJAR01/6115

RESEARCH ARTICLE

CASE REPORT: PSUEDO-THROMBOTIC THROMBOCYTOPENIC PURPRA AND COBALAMINE DEFICIENCY.

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Manuscript Info

Manuscript History

Received: 20 October 2017
Final Accepted: 22 November 2017
Published: December 2017

Keywords:-
B12 Deficiency, pseudo-thrombotic thrombocytopenic purpra, TTP, pancytopenia, Schistocyte

Abstract

Pseudothrombotic microangiopathy is thrombocytopenia, anemia and schistocytosis caused by Cobalamine deficiency. It could be easily misdiagnosed as microangiopathic hemolytic anemia.
Evaluation of lactate dehydrogenase, reticulocyte count, peripheral blood smear, platelet count, cobalamine and homocysteine level are crucial for differentiating pseudothrombotic microangiopathy from a true microangiopathic hemolytic anemia.
A case of pseudothrombotic microangiopathy due to severe vitamin B12 deficiency is presented.

Introduction:-

Thrombotic Thrombocytopenic Purpura (TTP) is characterized by microangiopathic hemolytic anemia, thrombocytopenia, and neurologic symptoms or renal injury with the disease process driven by a severe deficiency of ADAMTS13, metalloprotease and disintegrin that cleaves Ultra Large Von Willebrand Factor multimers (ULVWF). [1 2 3]

Vitamin B12 deficiency can present with microangiopathy and can be mistaken for TTP[4].

Inadequate consumption of animal foods is considered the most common cause of severe vitamin B12 deficiency worldwide in pediatric age group [5]. Most of the Cobalamine deficient cases have only mild haematological findings, in approximately 10% of patients presents with severe anemia, pancytopenia and hemolytic anemia[6].

Case report:-

A 2 years old boy was admitted to hospital with decreased oral intake, decreased appetite, fever and vomiting once. On examination the patient looked pale, apathy, weak; weight and height below 5th centile; and his sclerae were icteric. Laboratory investigations revealed macrocytic anemia (hemoglobin 6.6g/dl; leukopenia (neutrophil1300);and thrombocytopenia (58000). Reticulocyte count was 0.039. Lactate dehydrogenase (LDH) was 3707u/l. Direct Coombs and glucose-6-phosphate dehydrogenase deficiency tests were all negative. Alkaline phosphatase was high 991.7u/l. Plasma homocysteine level was elevated 27.6. A peripheral blood smear showed schistocytes and hypersegmented neutrophils .B12 level was 77.12pg/ml. folate serum was normal. Vitamin D was low and serum Iron was normal. ADAMTS13 was normal. Bone marrow aspiration study demonstrated megaloblastic erythropoiesis and ruled out leukemia. Intramuscular cyanocobalamin was started and patient respond very well.

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Discussion:-

Inadequate consumption due to dietary restriction or unavailable access to animal sourced food is the most common cause of Vitamin B12 deficiency in infants and children.[6]
In our patient, he was on exclusive breastfeeding. His four year-old sister presented 8 months later with decreased activity and appetite, and vomiting with evidence of hemolytic anemia and pancytopenia. Her lab consisted with elevated LDH (6310 U/L) and Schistocytes in peripheral blood smear, and low vitamin D.

Cobalamine deficiency is relatively common in the general population, with prevalence estimates ranging from 4-15%, it should be considered in the differential diagnosis of patients with microangiopathic hemolytic anemia.[2] [7]

In vitamin B12 Deficiency pseudothrombotic microangiopathy is related to ineffective erythropoiesis & intramedullary destruction of erythrocytes.[8]

In addition to intramedullary haemolysis, homocysteine accumulation due to vitamin B12 deficiency was found to increase haemolysis in vitro.[9] [10] pseudothrombotic microangiopathy presents in 2.5% of patients exhibited In one study of 201 patients with vitamin B12 deficiency.[7]

Its association with Vitamin B12 deficiency has been reported most frequently in adults with pernicious anaemia rather than in those with dietary insufficiency. [7] [11]

Cobalamin is essential co-factor for DNA synthesis and haematopoiesis, and its severe deficiency causes Neutropenia, thrombocytopaenia, & megaloblastic anaemia, as the case in our patient.[12] [13] [14] (table1)

Our patient had severe pancytopenia and findings of haemolysis (fragmented Red blood cells & polychromasia) in the peripheral smear mimicking microangiopathic haemolytic anaemia, low reticulocytes in relation to anemia and marked increase in Alkaline phosphatase & LDH.

Many authors reported a decreased absolute reticulocyte count, and a markedly elevated LDH favor the diagnosis of vitamin B12 deficiency (Psuedo-thrombotic Microangiopathy) over TTP. [2] [7] [11]

An LDH value exceeding 3000 U/L strongly favors pernicious anemia. [2]
We found an increase in LDH level of 3707 U/L in our case.

Furthermore there was dietary and family history of low vitamin D which rises a high suspicion of Nutritional B12 deficiency.

Plasma exchange has no rule in the treatment of B12 deficiency-induced pseudo-TTP.[15]

B12 deficiency, responds dramatically to oral or parenteral vitamin B12 .[11]

Reticulocyte counts reportedly respond to Vitamin B12 administration usually by day five, and the available data suggests that administration of vitamin replacement therapy in such cases is enough without any further intervention. [7] [16]

We achieved a reticulocytes response in our patient together with alkaline phosphatase & hemoglobin & decrease in LDH after five days of administration of parenteral Vitamin B12.

However platelet improved by day nine, and we noted a response in absolute Neutrophil Count by day fifteen.

Conclusion:-

Pseudo- TTP secondary to B12 deficiency should be in the differential diagnosis of patient presenting with microangiopathic hemolytic anemia in childhood.

We highly recommend performing B12 level, homocysteine level, LDH, reticulocyte count & reviewing peripheral blood smear in suspected TTP cases.

Acknowledgment:-

The authors declare no conflict of interest.

Age	Gender	Clinical Presentation	Lab
31 years [17]	Male	SOB, Fatigue and tingling sensation, inability to cooperate to complete Neurological Exam.	Hb: 4.4g/dL MCV:100.6fL PLT:87K/cmm Total Bilirubin: 2.7mg/dL Ind. Bilirubin: 1.9mg/dL LDH >665 U/L Haptoglobin: <7.8mg/dL Normal Coagulation profile Peripheral Blood Smear: Schistocytes Cbl: 68 pg/mL
12 months [18]	Male	Fatigue, bruise & pallor	Hb:7g/dL Hct:20.2% WBC:11.000/mm³ PLT:70.000/mm³ MCV:92.5fL Peripheral Blood Smear: RBC Macrocytic, Hypersegmented Neurtrophils. Cbl: 93pg/mL BMA: Megaloblastic changes
16 months [18]	Female	Fatigue, Bruise & pallor. Received PRBC transfusion from another center due to Low amount of RBC.	Hb:14.2g/dL Hct:44.6% (after transfusion) WBC:6.800/mm³ PLT:26.000/mm³ MCV:92.6 fL Peripheral blood smear: Macrocytic RBC, Hypersegmented Neutrophils BMA: Megaloblastic changes
14 years [16]	Female	Chronic Abdominal Pain, vomiting and pallor	Hb: 6.5g/dL WBC: 2.200/µl ANC: 968/µl PLT:62.000/µl Peripheral Blood Smear: Normal White Cells, No atypical lymphocytes, blasts or hypersegmented Neutrophils. BUN: 16mg/dl Creatinine: 0.7mg/dl Total Bilirubin: 2.7 mg/dl Direct Bilirubin: 0.8mg/dL LDH: 3454 U/L Uric Acid: 3.8 mg/dL DCT:Negative BMA: Normoblastic trilineage Hematopoisis Cbl: 75 pg/ml
8 months [19]	Female	Pallor, Vomiting, Diarrhea & Failure to thrive	Hb: 6.5g/dL WBC: 5.3x10³/µL ANC:0.42x10³ MCV:96.2 fL PLT: 147x10³/µL Peripheral Blood Smear: Macroovalocyte, Microcytes, Basophilic stippling and rare hypersegmented Neutrophils. BMA: hypercellular with absolute erythoid Hyperplasia, Megaloblastic Erythoid and myeloid maturation, dyserthropoiesis and dysgranulopoiesis. Cbl: <30 pg/mL
42 years [20]	Female	Fatigue, weakness	Hb:2.4g/dL Retic:4% WBC: 5.5x10³/µL PLT:42x10³/µL LDH: >2500 U/L Haptoglobin: <10 mg/dL TIBC: 263 µg/dL Iron saturation:60% CbL: 46pg/mL
42 years [21]	Male	Weight loss 6-8 pounds over 2 months, fatigue, presyncope, pale mucous membrane & Diabetic Ketoacidosis.	Hb:8.1g/dL WBC: 4100cells/mm³ MCV: 107.1 µm³ PLT: 39,000cells/mm³ RDW:19 Ind. Bilirubin: 1.6mg/dL Peripheral blood smear: Macrocyte, 3+ Schistocytes, hypersegmentend Neutrophils and very few Platelets.

			Serum Iron: 174µg/dL TIBC: 199µg/dL iron Saturation: 87.4% Cbl: 159 pg/mL
77 years [2]	Female	Altered mental status, nausea, vomiting , bowel incontinence and bloody diarrhea	Hb: 55 g/L MCV:120 fL WBC:5.9x10^9/L PLT:40x10^9/L Peripheral blood smear: Anisocytosis, Poikilocytosis & multiple schistocytes. Creatinine: 300µmol/L LDH:3981 IU/L DCT: negative Cbl: undetectable
31 years [22]	Female	Fatigue, Paresthesia, Scleral icterus and pallor	Hb: 5.7 g/dL Hct:15.7% WBC:4,200/mm³ PLT:81,000/mm³ Total Bilirubin: 2.2mg/dL Direct Bilirubin: 0.5mg/dL LDH: 4579 U/l Peripheral blood smear: Numerous schistocytes, anisocytosis, & Macro-ovalocytes. Cbl: 125pg/mL MMA: 6258 mmol/L
86 years [23]	Female	Altered mental status, intubated in ER due to respiratory distress	Hb: 3.2g/dL Hct: 9.6% MCV: 127 fL Retic: 7.5% WBC: 6.5x10³/µL PLT: 59x10³/µL LDH: 7077 IU/L Haptoglobin: 14mg/dL BUN: 34mg/dL Creatinine: 1.9mg/dL Peripheral blood smear: large RBC, Hypersegmented Neutrophils, 1% schistocytes, Poikilocytes, & Anisocytes. Cbl: 38 pg/mL MMA: 753nmol/L Homocysteine:99.3µmol/L
36 years[24]	Male	Fatigue, poor exercise tolerance.	Hb: 7.9g/dL MCV: 104.4 fL Retic: 1.6% WBC: 3300/mL PLT: 157,000/µL Bilirubiin: 1.2 mg/dL DCT: Negative Peripheral blood smear: Red cell fragmentation, schistocytes, prominent anisopoikilocytosis with teardrop cells, macroovalocytes, & rare hypersegmented Neutrophils LDH: 3988 U/L Haptoglobin: <30mg/dL BMA: Macrocytic Anemia, mild hypercellularity with trilineage dysplasia & a shift towards immaturity. Cbl: 111pg/mL MMA: 19.69mM/L Homocysteine:181.3µM/L
35 years[25]	Male	Progressive pallor, headache, fever & red colored urine. On physical examination: pale, jaundice and there was patechia on the extremities and trunk	Hb: 5 g/dL Retics: 30% WBC: 4.4x10^9/L PLT: 12x10^9/L Peripheral blood smear: Polychromasia, oval & crenated cells & many fragmented cells. DCT: Negative G6PD: Deficient LDH: 2250 U/L Liver and renal function: Normal BMA: Erythroid hyperplasia.
15 years [26]	Female	Status Epilepticus, Loss of consciousness, unable to control urination. CT abdomen: slight swelling of the liver with edema around portal vein.	Hb: 2.5g/dL MCV: 128.8 fL Retic: 8.7% WBC: 11600/mm³ PLT: 53000/mm³ Peripheral blood smear: hypersegmented Neutrophils, red cell Microcytes, Schistocytes, teardrop cells & macrocytes. LDH: 1903 U/L

			BMA: Active Hyperplastic trilineage hematopoiesis with a markedly increased number of large immature erythroblasts. Cbl: 104 pg/mL Folic Acid: 1.4 ng/mL
15 years [27]	Male	Vegetarian boy with easy fatigue, breathlessness, pain on the legs on walking. Paleness and icterus in the sclera. Abdominal U/S: Splenomegaly: 130 mm in length	Hb: 5.1 g/dL MCV: 116 fL Retic: 0.8% WBC: 2540/µL ANC: 1230/µL PLT: 107,000/mm³ LDH: 5565 U/L Peripheral blood smear: Anisocytosis, Poikilocytosis with macrocytes and small fragmented red cells. BMA: Macromegaloblastic Erythropoisis. Cbl: 52 pg/mL Homocyteine: >50 µmol/L
33 years [28]	Female	Woman in 2nd pregnancy with Gestational Age of 37 weeks and 3 days.	Hb: 7.2 g/dL Hct:22.2% MCV: 103fL WBC:9500/µL PLT: 42000/µL Peripheral blood smear: Slight hypochromia with Macrocytosis

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