ORIGINAL RESEARCH PAPER

Volume-7 | Issue-3 | March-2018 | PRINT ISSN No 2277 - 8179

INTERNATIONAL JOURNAL OF SCIENTIFIC RESEARCH

'FACTOR DEFICIENCY IN GAUCHER'S DISEASE – DIAGNOSTIC AND THERAPEUTIC CHALLENGES'

Pediatrics

Dr.Jesu Magdalene Post Graduate Student

Dr. R Aruna Assistant Professor, Paediatric haematology

Dr.Sai Shalini Associate Professor of Pathology

Dr.D.Febe Renjitha Suman* Professor of Pathology, *Corresponding Author

ABSTRACT

A 2 year old boy diagnosed as Gaucher's disease had factor IX deficiency and transient lupus anticoagulant .Splenectomy followed by BMT was done with supportive Factor IX concentrate. Engraftment of donor BMT led to success in the treatment.

KEYWORDS

INTRODUCTION:

This is a autosomal recessive lysosomal storage disorder in which glucocerebrosides accumulate in the macrophages of liver,spleen and bone marrow due to inhertited deficiency of lysosomal acid beta glucosidase caused by mutation in GBA1 gene located at 1q 21.We present a case of Gaucher's disease with thrombocytopenia ,transient lupus anti coagulant and factor IX deficiency.

CASE REPORT:

A two year old male baby was admitted for splenectomy.He was born of spontaneous vaginal delivery, had normal developmental mile stones, immunised according to schedule.There was history of second degree consanguineous marriage between the parents.The baby was well till one and half years of age .He was investigated for hepatosplenomegaly and diagnosed as Gaucher's disease due to beta glucosidase enzyme deficiency which was 0.24 nmol /g/hr at the time of investigation (Reference value>= 8.7nmol/mg/hr <15 % indicates Gaucher's disease) .On examination the patient was malnourished with 7.3 kg which is less than 3rd percentile. He was pale, and his vital signs were within normal limits. His cardiovascular, respiratory and neurologic examination was within normal limits. Abdominal examination showed hepatomegaly extending 2 cm below the costal margin and massive splenomegaly, the spleen descending till the right iliac fossa .Ultrasonography of the abdomen showed multiple infarcted areas in spleen.In view of massive splenomegaly due to Gaucher's disease it was decided to perform splenectomy after presurgical screen and immunisation.

Pre splenectomy haematological workup showed haemoglobin 7 g/dl,red blood cell(RBC) count 2.83 million cells/cumm,WBC 4500cells /cumm, differential counts being polymorphs 32.8%,lymphocyte 56.7% eosinophils 2.8 %monocyte7.1 % ,and platelet count 30000 cells/cumm. The coagulation profile showed prothrombin time (PT) 15.1 seconds, activated partial thromboplastin time (APTT) 68.50 seconds .The liver function tests and renal function tests were within reference ranges,In view of the prolonged APTT and thrombocytopenia the patient was transfused with fresh frozen plasma (FFP) and platelets for 4 days. In spite of this repeated transfusion the APTT was prolonged to 72 seconds.Hence differential diagnosis of disseminated intravascular coagulation (DIC),liver disease,massive transfusion,factor inhibitor and factor deficiency were made. The liver function test, PT and thrombin time were normal and transfused with FFP and platelets the possibility of DIC, liver disease and massive transfusion were not considered. The APTT clot wave was analysed with sysmex CS2400 coagulation analyser for the test with and without mixing of plasma (figure 1).The clot wave represented as that of a major factor IX deficiency and with an inhibitor .The factor assays showed low factor IX of 16 %(normal > 60 %) and positive lupus anticoagulant test with APTT& diluted Russell viper venom test(dRVVT) the patient .The patient was transfused factor IX concentrate 100 units /kg /dose 12 th hourly for 4 days.

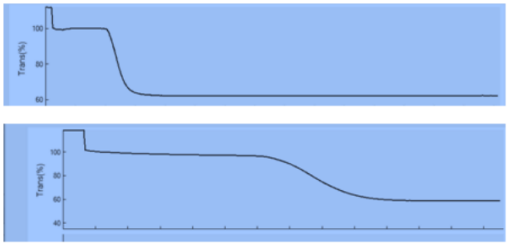

FIGURE: 1

A- Normal APTT clot wave form
B- APTT Clot wave with factor IX deficiency &transient lupus

Splenectomy was done with intraoperative factor IX infusion. The spleen was sent for histopathological examination .Grossly the spleen measured 18x15x6 cm, external surface was grey black and cut surface showed pale infarcted areas. Microscopically multiple sections of spleen studied showed widening of red pulp with enlarged histiocytes having abundant fibrilary granular cytoplasm, and peripherally pushed nuclei. White pulp was unremarkable .Large areas of necrosis was noted .Special stains for Periodic acid–Schiff (PAS), Periodic acid–Schiff Diastase (PAS-D) was positive and immunohis tochemistry showed cytoplasmic positivity to CD 68.Histopatholgy was consistent with Gaucher's disease (figure 2).On day 15 th of splenectomy, APTT was still prolonged and Factor IX was low as 21 % and lupus anticoagulant was negative.

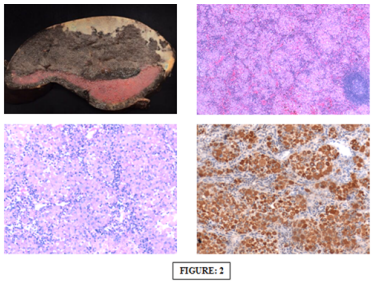

FIGURE: 2

A. Gross image of cut surface of spleen showing infracted area.
B. Sheets of Gaucher's cells (Hematoxylin & Eosin ,40 X).
C. PAS positive Gaucher's cells (PAS, 40 X).
D. Immunohistochemistry(IHC) ,cytoplasmic positivity to CD 68(IHC,10 X)

One and half month's later bone marrow transplantation (BMT) was done with donor being healthy elder sibling. On day 20 of BMT, PT was 14 seconds, APTT was 24.70 seconds. On day 60 Factor IX was 59 % and chimerism was 71 % and the child was discharged on day 62 .On follow up after 3 months of BMT glucocerebrosidase enzyme level was normal.

DISCUSSION:

Gauchers disease was first described by Philippe Gauchers in 1882[1].This disease has a worldwide incidence of 1 in 100000[2].In India it is found to be prevalent in Mapila muslims of kerala[3],The patient present in early childhood with hepatosplenomegaly and hematologic abnormalities with pancytopenia and leukoerythrobastic reaction .The index case presented with thrombocytopenia ,transient lupus anti coagulant & factor IX deficiency.The patient did not have bleeding complications in spite of severe thrombocytopenia and factor IX deficiency.Thrombocytopenia in Gaucher's disease is due to hypersplenism and or bone marrow infiltration by Gauchers cells which can compromise megakaryopoiesis[4].It has been reported that Gaucher's disease may be associated with immunological disorder which leads to immune thrombocytopenia.In our case the immune mechanism may not be the cause as there was platelet recovery after splenectomy [5].Reduced activity of coagulation factors have been reported in Gaucher's disease ,the most common factor affected was found to be factor V the others being Factor X, II.The other deficiencies encountered were factor VIII and II[6] .In a study done on 30 patients by Hollak et al factor IX deficiency was not observed though the other factor deficiencies were present[7]. The same observations were made by Billet et al in 1996[8].In 1976 Boklan and Sawitsky hypothesised low grade intravascular coagulation being the cause for reduced factor IX in his series of patients[9].In our case isolated factor IX deficiency was present.It has been hypothesised a reduction in concentration of clotting factors is associated with enlarged spleen as well as liver which are infiltrated by Gaucher's cells[10]. Hepatocyte dysfunction may been the eitology factor in coagulation factor deficiency ,but it has been found that the hepatocytes function has been preserved.It has been reported that an enhanced ongoing low grade activation of coagulation especially in patients with splenomegaly may be the cause for factor deficiency ,this enhanced coagulation being due to increased mononuclear cell infiltrate as Gaucher cell burden releases tissue factors and pro inflammatory cytokines resulting in overt DIC. But in our case the enlarged spleen may not be the cause for factor IX deficiency as the APTT was not corrected after splenectomy .It was corrected only after BMT .

Lupus anticoagulant was positive in our case which may either be a transient lupus anticoagulant or may be due to cerebroside competing with phosholipid[11].The analysis of APTT clot wave in the recent automated coagulation analyser is a challenge and expertise is need to guide for further work up.In this case the clot wave was the major guiding tool . However in our case the lupus anticoagulant was negative before BMT, indicating this as a transient one.

The treatment strategies in Gaucher's disease are substrate reduction therapy, enzyme replacement therapy,or bone marrow transplant .Substrate depletion is usually advocated for milder disease when enzyme replacement therapy is not possible .This is mainly used as maintenance therapy [12].Enzyme replacement therapy is the standard replacement therapy in Gauchers disease[13]. However the enzyme replacement cost US$100,000-US$ 200,000/year[14]. In our case BMT was considered due to economic constraint but found to be successful as the enzyme level was raised and Factor IX deficiency was corrected.

Investigation for Gaucher's disease to be done in children with massive splenomegaly . Presurgical work up for hemostatic abnormalities to be done as factor deficiencies can occur in Gaucher's disease.However the identification of the deficient factor is essential for replacement therapy with the factor concentrate as well to avoid FFP transfusion. BMT is a successful therapeutic option in resource constraint situation. This case is presented for its rarity,and diagnostic and therapeutic challenges encountered for a successful outcome.

CONFLICTS OF INTEREST:

The authors declare no conflict of interest.

REFERENCES

1. Aabha Nagral Gaucher diseasejournal of clinical and experimental hepatology j clin exp hepatol 2014;4:37–50
2. Beutler E, Grabowski GA. Gaucher disease. In: Scriver CR,Beaudet AL, Sly WS, Valleeds. Metabolic and Molecular Bases of Inherited Disease. New York: McGraw-Hill; 2001:3635.
3. Feroze M, Arvindan KP, Jose L. Gaucher's disease among Mappila muslims of Malabar. Indian J Pathol Microbiol. 1994;37:307–11. [PubMed: 7814063]
4. Stein P, Malhotra A, Haims A, et al. Focal splenic lesions in type I Gaucher disease are associated with poor platelet and splenic response to macrophage-targeted enzyme replacement therapy. J Inherit Metab Dis 2010;33:769–74.
5. Rosenbaum H, Napso T, Bonstein L. Immune thrombocytopenia in type I Gaucher disease. Blood 2007;110:3200a.
6. Carla E.M.Hollak,Marcel Levi,Fenny Berends,Johannes M.F.GAerts and Marinus H.J. Van Oers Coagulation abnormalities in type 1 Gaucher's diseade are due to low grade activation and can be partly restored by enzyme supplement therapy. Br J Haematol 1997;96:470–476.
7. Hollak CE, Levi M, Berends F, et al. Coagulation abnormalities in type 1 Gaucher disease are due to low-grade activation and can be partly restored by enzyme supplementation therapy. Br J Haematol 1997;96:470–6.
8. Billet H,Rizvi,S.&sawitsky A. (1996)Coagulation abnormalities in patients with Gaucher's disease:effect of therapy, American Journal of Haematology51,234-236
9. Boklan,B.F& Sawitsky A.(1976)Factor IX in Gaucher's disease.Archives of Internal medicine 136,489-492.
10. Gerritis WBJ.,Van Aken,G.,van der Meer,J.&Vreeken,J.(1974)splenomegaly associated with chronic consumption coagulopathy.ActaMedicaScandinavica,195,245-430.
11. Cox TM, Aerts JM, Andria G, et al. The role of the iminosugar N-butyldeoxynojirimycin (miglustat) in the management of type I (nonneuronopathic) Gaucher disease: a position statement. Advisory Council to the European Working Group on Gaucher Disease SOJ Inherit Metab Dis. 2003;26:513–526.
12. Elstein D, Dweck A, Attias D, et al. Oral maintenance clinical trialwith miglustat for type I Gaucher disease: switch from or combinationwith intravenous enzyme replacement. Blood. 2007;110:22962301
13. Zimran A, Brill-Almon E, Chertkoff R, et al. Pivotal trial with plant cell-expressed recombinant glucocerebrosidase, taligluceraseالfa, a novel enzyme replacement therapy for Gaucher disease.Blood. 2011;118:5767–5773.
14. Vijay Bohra and Velu Nair Gaucher's disease Indian J Endocrinol Metab. 2011 Jul-Sep; 15(3): 182–186.