Case Report

A Rare Case Report of Factor IX Deficiency

Sri Hala.N [1], Aparna Matpathi*[1], Dr. Ramya Bala Prabha. G[2].
1. Doctor of Pharmacy Intern, CMR College of Pharmacy, Telangana, India.
2. Associate Professor of department of Pharm D, CMR College of Pharmacy, India.
***Corresponding author's E-mail:** aparnamatpathi@gmail.com

Received: 21-05-2023; **Revised:** 24-07-2023; **Accepted:** 30-07-2023; **Published on:** 15-08-2023.

ABSTRACT

This case study represents a childbearing 3 months of age with prolonged bleeding after injury, with history of Factor IX deficiency along with general tonic clonic seizures. Factor IX deficiency is also known as Hemophilia B, which is a rare inherited disorder affecting 1 in 25,000 male births. It occurs due to mutation in the F9 gene which is responsible for production of Factor IX. This report provides an insight of challenges associated with managing the condition including differential diagnosis, treatment strategies to be employed as currently no treatment option is available to reverse this rare genetic disorder. It provides the information which contributes in improving the medical literature, to enhance of knowledge of healthcare professionals and the immediate family members of the patients as they play a key role in taking care of patient outside the hospital setting.

Keywords: Hemophilia B, Factor IX deficiency, mutation in F9 gene, serum iron, serum ferritin levels, fresh frozen plasma transfusion, Vitamin-K.

INTRODUCTION

In this case report we present a case that manifested with pediatric onset of factor IX deficiency. Factor IX deficiency is an alternate term used to refer the condition, which was initially named as "Christmas disease" in honor of the first individual diagnosed with it in 1952 [1]. Factor IX deficiency, also known as hemophilia B, is an inherited disorder affecting blood coagulation. Carriers are usually females with one defective factor IX gene, and they do not exhibit symptoms. However, male offspring of carriers have a 50% chance of developing the disease, while female offspring have a 50% chance of becoming carriers themselves. The condition stems from a deficiency of a specific blood plasma protein called factor IX. Insufficient levels of factor IX impair blood clotting, leading to difficulty in controlling bleeding [1]. Hemophilia B has an incidence of around 1 in 25,000 male births [2]. While a significant number of females who carry the hemophilia B gene may not exhibit any symptoms, approximately 10-25% of them are estimated to experience mild symptoms. It has also been documented that females can present with moderate to severe symptoms of the condition [2]. The diagnosis of hemophilia B involves considering several factors, including the patient's personal bleeding history, their family's bleeding history and inheritance patterns, and conducting laboratory tests [2]. Hemophilia B is marked by a deficiency in factor IX clotting activity, leading to persistent oozing following injuries, tooth extractions, or surgical procedures. It also causes delayed or recurring bleeding before wounds fully heal [3]. Severe hemophilia B is typically identified within the first two years of life. In the absence of prophylactic treatment, individuals with severe hemophilia B may experience an average of two to five spontaneous bleeding episodes per month. These episodes can manifest as spontaneous joint or muscle bleeds, as well as prolonged bleeding, excessive pain, and swelling following minor injuries, surgeries, and tooth extractions [3]. Moderate hemophilia B is characterized by infrequent spontaneous bleeding, although the frequency can vary among individuals. Instead, individuals with moderate hemophilia B typically experience prolonged or delayed oozing following minor trauma. Diagnosis of moderate hemophilia B typically occurs before the age of five to six years. The frequency of bleeding episodes can range from once a month to once a year [3]. Individuals with mild hemophilia B do not typically experience spontaneous bleeding episodes. However, in the absence of appropriate pre- and postoperative treatment, abnormal bleeding can occur during surgical procedures or tooth extractions. The frequency of bleeding episodes for those with mild hemophilia B can vary, ranging from once a year to once every ten years. It is common for individuals with mild hemophilia B to receive a diagnosis later in life [3]. The F9 gene is responsible for Hemophilia B as mutations in this gene disrupt the production of factor IX. The F9 gene is specifically situated on the long arm of the X chromosome at position Xq27.1 [4].

The purpose of reporting this case study is to enhance medical knowledge and to improve patient care, to contribute to the existing medical literature, to bring awareness about this condition, highlight the diagnostic criteria which helps to differentiate hemophilia B from other clotting disorders which provides valuable insight in clinical practice. Transfusions of fresh frozen plasma along with vitamin K injections have been shown to be beneficial in promoting blood clot formation.

CASE STUDY

A 3-month-old child was brought to the outpatient department, he was second-born in a non-consanguineous

marriage. Initially, the child appeared asymptomatic until reaching 2 months of age when he experienced a generalized tonic-clonic seizure. The seizure activity persisted for 30 minutes without regaining consciousness in between. Upon arrival at the hospital, the child was immediately intubated, and intravenous anti-epileptic drugs, antibiotics, and supportive therapy were administered. After four days, the child's condition improved, and extubation was performed. Additionally, he also suffered with prolonged bleeding followed by any injury. The child had a history of Factor IX deficiency and came for follow up.

Laboratory Investigations

The investigations conducted on the child revealed several abnormalities. These include increased total serum bilirubin, decreased hemoglobin levels, elevated liver enzymes, prolonged activated partial thromboplastin time (APTT), prolonged prothrombin time (PT), and deranged international normalized ratio (INR). A CT scan showed the presence of a left frontal subdural hematoma and subarachnoid hemorrhage. Further evaluation revealed a deficiency in factor IX. Neurosurgical examination revealed asymmetrical dilation of the left ventricle, suggesting exvaeno dilatation, as well as a prominent extra axial subdural collection/hygroma on the left side. A 2D-Echo revealed fair left ventricular and right ventricular function. An electrocardiogram showed sinus tachycardia, a short PR interval, right ventricular hypertrophy, and borderline abnormal T-wave changes suggestive of age and gender abnormalities. Hepatic-A IgM present.

Table 1: Table depicting laboratory investigations

S. No	Name of the diagnostic procedure	Abnormal values	Normal range
1.	Blood urea nitrogen	6.2mg/dl	7.0-20.0mg/dl
2.	Urea	13.19	5-18 mg/dL
3.	Creatinine	0.09mg/dl	0.7-1.4mg/dl
4.	Alanine transaminase	233.5U/L	7-55U/L
5.	Aspartate aminotransferase	136U/L	5-40U/L
6.	Aluminum phosphate	485.4U/L	40-150U/L
7.	Total bilirubin	2.44mg/dl	0.3-1.0mg/dl
8.	Phosphate	5.2mg/dl	2.5-4.5mg/dl
9.	Direct bilirubin	1.2mg/dl	0.1-0.3mg/dl
10	Sodium	113mmol/l	135-145mmol/l
11.	Potassium	5.4mEq/l	3.6-5.2mEq/l
12.	Chlorine	88mmol/l	96-106mmol/l
13.	Alpha-fetoprotein	9142ng/ml	<7ng/ml
14.	Serum iron	174mg/dl	40-100mg/dl
15.	Serum ferritin	1327ng/ml	22-322ng/ml
16.	Lactate dehydrogenase	219U/L	160 to 450U/L

Based on all the investigations, thorough examination and laboratory data it was confirmed that the patient was suffering with “Factor IX Deficiency”.

Treatment

The patient underwent a series of fresh frozen plasma transfusions to address the deficiency of a coagulation factor and halt the bleeding. Additionally, he received injection Vitamin K 5mg IV once daily to promote the production of prothrombin, a vital component in blood clotting. To manage seizures, the patient was prescribed syrup phenobarbitone 5mg/kg/day and syrup levetiracetam 30mg/kg/day. Ciprofloxacin eye drops were administered three times daily to relieve ocular concerns.

For nutritional support, the patient received Multivitamin drops orally once daily, along with 1ml of vitamin D3 drops orally once daily. To alleviate abdominal pain, the patient was given Hyoscine butyl bromide syrup 80mg/kg/day.

DISCUSSION

In this case, a 3-month-old child with a history of factor IX deficiency was presented. The child received treatment with fresh frozen plasma and a vitamin K injection to prevent bleeding. These interventions proved effective in preventing bleeding episodes and managing the child's condition. Hemophilia B is a severe inherited bleeding disorder with significant clinical implications [4]. The estimated birth prevalence of hemophilia B is five in 100,000 live male births, with severe hemophilia B occurring at a rate of 1.5 in 100,000 [3]. Currently, there are no viable treatment options available for Hemophilia B, leading to significant rates of mortality and disability. Consequently, it is of utmost significance for carriers of the condition to engage in genetic counseling and undergo prenatal diagnosis [4].

Factor IX is produced by hepatocytes and is classified as a component of the intrinsic pathway within the coagulation cascade. Insufficient levels of factor IX lead to impaired clotting and the inadequate formation of a fibrin mesh [5]. The human FIX gene is located on the X chromosome and consists of 8 exons, spanning a length of 33.5 Kb. Mutations in this gene can interfere with the normal functioning of the F-IX protein, leading to the bleeding disorder known as hemophilia B [6]. Previously, the primary treatment for hemophilia B involved intermittent plasma transfusions, which were later replaced by more efficient prothrombin complex concentrates. PCCs contain a combination of vitamin K-dependent pro-coagulation factors, such as FII, FVII, and FX. However, a notable disadvantage of PCCs is the potential risk of thrombotic events [6]. More refined forms of Factor IX have been obtained by isolating them through Cohn fractionation using ion-exchange chromatography [6]. The safety of F-IX plasma concentrates is further constrained by the presence of detectable levels of activated F-IX (F-IXa) and residual amounts of other pro-coagulation factors, which contribute to a notable risk of thrombotic events. However, the implementation of immunoaffinity

purification for plasma-derived F-IX has proven effective in addressing these limitations [6]. Nonacog alpha, marketed under the trade name Benefix, stands as the sole commercially available recombinant F-IX medicinal product to date. It received approval for clinical use in both the United States and the European Union in 1997 [6]. The product is prepared as a lyophilized powder formulation that does not contain human serum albumin [6]. Enhancing the pharmacokinetic characteristics of F-IX can be achieved by genetically combining it with extended-lasting plasma proteins or chemically attaching hydrophilic polymers through covalent conjugation [6]. As per the present data no treatment is helpful in reversing the condition all the therapies could be employed only to provide relief to the patient and to improve the blood clotting as this disorder is caused due to mutation in F9 gene.

The primary objective of presenting this case report is to raise awareness among healthcare professionals regarding the potential complications linked to the diagnosis and treatment of this condition. Additionally, it aims to educate patients, family members, and caregivers about preventive measures to avoid such disorders and promote early recovery for alleviating symptoms, considering that a permanent cure is currently unavailable for this condition.

CONCLUSION

Hemophilia B is very rare in occurrence and various challenges are involved in diagnosing the disease as it may resemble disorders of other coagulation factors. Treatment options require further research as currently employed treatments are associated with various unwanted outcomes. It is crucial to explore safer and more effective treatment options to improve the health of patients and aid faster recovery. Providing education to caregivers and immediate family members about this condition is essential, as they play a vital role in offering necessary care, attention, and support, which greatly contributes to the patient's recovery.

Abbreviations:

1. F-IX – Factor IX
2. IV- Intravenous
3. PCC- Prothrombin complex concentrates
4. CT Scan- Computed tomography scan
5. 2D Echo- 2D Echocardiogram
6. Ig M- Immunoglobulin M
7. APTT- Activated partial thromboplastin time
8. PT- Prothrombin time
9. INR- International normalized ratio

Acknowledgements: All the authors humbly show their gratitude towards Dr. Rama Rao Tadikonda for providing his valuable knowledge and helping us in writing the manuscript.

REFERENCES

1. Philip J, Sarkar RS, Kumar S, Prathip BR, Pathak A. Factor IX deficiency (Christmas disease). Med J Armed Forces India. 2012;68(4):379-80. doi: 10.1016/j.mjafi.2011.12.007, PMID 24532909.
2. George C, Parikh S, Carter T, Morris A, Cramey C, Mcelroy K et al. Hemophilia B. Haemophilia. 2023. doi: 10.1111/hae.14812, PMID 37335559.
3. Konkle BA, Nakaya Fletcher S. Hemophilia B. 2000 Oct 2. In: Seattle: University of Washington. Seattle. p. 1993-2023; Updated 2023 Feb 9. GeneReviews® [internet] Adam MP, Mirzaa GM, Pagon RA, et al., editors. Available from: https://www.ncbi.nlm.nih.gov/books/NBK1495/.
4. Lv X, Li T, Li H, Liu HY, Wang Z, Guo ZP. Genetic analysis of a hemophilia B family with a novel F9 gene mutation: a STROBE-compliant article. Medicine. 2019;98(21):e15688. doi: 10.1097/MD.0000000000015688, PMID 31124946.
5. Alshaikhli A, Rokkam VR. Hemophilia B. [Updated 2023 Apr 24]. In: StatPearls [Internet]. Treasure Island (FL): StatPearls Publishing; 2023 Jan-. Available from: https://www.ncbi.nlm.nih.gov/books/NBK560792/
6. Orlova NA, Kovnir SV, Vorobiev II, Gabibov AG. Coagulation factor IX for hemophilia B therapy. Acta Nat. 2012;4(2):62-73. doi: 10.32607/20758251-2012-4-2-62-73, PMID 22872812.

Source of Support: The author(s) received no financial support for the research, authorship, and/or publication of this article.

Conflict of Interest: The author(s) declared no potential conflicts of interest with respect to the research, authorship, and/or publication of this article.