International Journal of Contemporary Pediatrics
Kannan P et al. Int J Contemp Pediatr. 2016 Aug;3(3):896-901
http://www.ijpediatrics.com
pISSN 2349-3283 | eISSN 2349-3291

DOI: http://dx.doi.org/10.18203/2349-3291.ijcp20162362

Research Article

A clinico haematological study of inherited bleeding disorders in children

P. Kannan[1], C. Anitha Mohan[2]*

[1]Institute of Child Health and Research Centre, Government Rajaji Hospital, Madurai, Tamil Nadu, India
[2]Institute of Physiology, Madurai Medical College, Madurai, Tamil Nadu, India

Received: 30 March 2016
Accepted: 09 May 2016

***Correspondence:**
Dr. C. Anitha Mohan,
E-mail: anithamohan76@gmail.com

Copyright: © the author(s), publisher and licensee Medip Academy. This is an open-access article distributed under the terms of the Creative Commons Attribution Non-Commercial License, which permits unrestricted non-commercial use, distribution, and reproduction in any medium, provided the original work is properly cited.

ABSTRACT

Background: The pattern of congenital bleeding disorders cases attending a tertiary level hospital is examined in this study by establishing their etiological diagnosis and providing appropriate management options for the disorders. This study aims to detect congenital bleeding disorder clinically among children between 3 months to 15 years of age, and to confirm and classify the types of bleeding disorders. This study gains importance in the scenario of recent advances in carrier detection and gene therapy for genetically inherited bleeding disorders.
Methods: This study comprised of 32 patients with bleeding manifestations attending pediatric outpatient department. They were examined for the clinical presentation and underwent hematological investigations to arrive at a diagnosis. The data thus obtained was tabulated and analyzed to study the demographic distribution and clinical presentation of the congenital bleeding disorders.
Results: In this study, amongst the hereditary bleeding disorders hemophilia was found to be the commonest congenital hemostatic defect. Factor VIII deficiency was the commonest (18 out of 32) bleeding disorder, followed by factor IX (3 out of 32). Six cases of platelet disorders were diagnosed of which 4 patients were diagnosed to have thrombasthenia. The commonest clinical manifestation was subcutaneous hematoma. 22 children complained of bleeding gums followed by spontaneous hemarthrosis (17 episodes). Long term complications of bleeding disorders like growth retardation, anemia, joint deformity and hemiplegia were also observed in the study.
Conclusions: Spreading awareness regarding bleeding disorders along with prompt diagnosis, appropriate treatment and follow up and genetic counseling is essential to prevent morbidity due to congenital bleeding disorders.

Keywords: Hemophilia, Coagulation disorder, Platelet, Thrombasthenia, Hemarthrosis

INTRODUCTION

Since Judah the Patriarch's first allusion to the disease in the Taimud in the 2nd century AD, the history of haemophilia has been a long journey through the triumphs and tragedies of transfusion therapy.[1] Once haemophilia was called a royal disease and Queen Victoria was a carrier. She was not the first to carry it; it has been on earth for centuries.[2]

Diagnosis and treatment of inherited bleeding disorders is now well established in developed countries. But in many developing countries the knowledge and facilities for accurate diagnosis and sustained therapy are lacking. Few children with severe haemophilia can expect to survive beyond adolescence and those too will have incapacitating painful arthritis. It has been estimated that by the year 2020 there will be around 5,50,000 people with haemophilia in the world who will have replacement therapy.[3]

Present study was under taken with an aim to study the pattern of congenital bleeding disorders coming to a tertiary level hospital and establishing accurately their etiological diagnosis. This study gains importance in the scenario of recent advances in carrier detection and gene therapy for genetically inherited bleeding disorders.

This study aims to detect congenital bleeding disorder clinically among children between 3 months to 15 years of age, and to confirm and classify the types of bleeding disorders namely (a) Coagulation disorder and (b) Platelet disorder and to counsel the above diagnosed patients.

METHODS

This study comprised of 32 patients with bleeding manifestations treated in the Department of Paediatrics, JIPMER, Pondicherry after obtaining approval from the ethical committee. The patients included in this study were both old cases and newly diagnosed cases of bleeding disorders. All these cases were clinically examined taking into consideration the history and clinical presentation. All these cases were investigated in the hematology section of Pathology Department, JIPMER.

Inclusion criteria

Already diagnosed and new cases of bleeding disorders between 3 months to 15 years of age.

Exclusion criteria

All acquired bleeding disorders (e.g.) snake bite, ITP and late hemorrhagic disease of new born.

Age and sex of the patients were noted. Family history and age of onset of bleeding disorder was noted. The clinical features with which the subjects presented were noted. The patients were subject to the following first line investigations : (1) Haemoglobin estimation using photoelectric colorimeter[4], (2) Bleeding time by Dukes method[5], (3) Clotting time by Lee-White method[5], (4) Clot retraction time, (5) Platelet count by direct method[6], (6) Prothrombin Time, (7) Activated partial thromboplastin time.[7]

Second line of investigations include: (1) Fibrinogen assay, (2) Thromboplastin Generation Test, (3) Thrombin Time, (4) Mixing experiment (5) Factor VIII assay based on the thromboplastin generation test, (6) Factor IX assay, (7) Factor XIII assay.[4]

RESULTS

Demographic features

Thirty two patients with congenital bleeding disorders were studied. Out of these 26 patients (81.25%) belonged to the group of clotting disorder. More than half of them (56.25%) were found to be suffering from Haemophilia A (Factor VIII deficiency). There were three patients (9.37%) with haemophilia B (Factor IX deficiency). There was one case of factor VII deficiency and one case of fibrinogen deficiency (Table 1).

Table 1: Demography of congenital bleeding disorders.

Disease	Number	%	Family history positive	%	Male	%	Female	%
Total cases studied	32							
Clotting disorder	26	81.3	9	28.12	24	74.88	2	6.25
Hemophilia A	18	56.3	1	3.12	18	56.16	-	-
Hemophilia B	3	9.4	2	6.25	3	9.37	-	-
Factor XIII deficiency	3	9.4	-	-	2	6.25	1	3.12
Factor VII deficiency	1	3.1	-	-	-	-	1	3.12
Fibrinogen deficiency	1	3.1	-	-	1	3.12	-	-
Platelet disorder	6	18.72	4	12.5	3	9.37	3	9.37
Thrombasthenia	4	12.5	2	6.25	2	6.25	2	6.25
Bernaud Soulier syndrome	2	6.2	2	6.25	1	3.12	1	3.12

Amongst the children with clotting disorders about 1/3 (28.12%) had family history of similar illness. There were 18 males afflicted by factor VIII deficiency and three boys had factor IX deficiency. Three cases of factor XIII deficiency comprising of 2 males and one female patient were also detected. One female child was found to be suffering from factor VII deficiency and one boy had fibrinogen deficiency. Six cases of platelet disorders were diagnosed of which 4 patients (6.25% 2 females and 2 males) were diagnosed to have thrombasthenia. Positive

family history was elicited in two children. Two siblings' brother and sister were found to have Bernard-Soulier syndrome.

Age of onset bleeding

16 children out of 32 (50%) had onset of bleeding less than 1 year of age out of these, 10 patients had their first bleeding episode below 6 months of age. 6 children manifested their first bleeding episode between 6 months to 1 year of age. 13 children (40.62%) had first bleeding episodes below 5 years of age. Only 3 children had their first symptoms beyond 5 years. Thus majority of patients had their onset of first bleeding episode below 5 years of age (Table 2).

Table 2: Age of onset of bleeding.

Age of onset	Hemophilia A		Hemophilia B		Factor XIII deficiency		Factor VII deficiency		Fibrinogen Deficiency		Platelet disorder	
	No.	%	No.	%	No.	%	No.	%	No.	%	No.	%
0-1	9	28.12	2	6.25	2	6.25	-	-	1	3.12	2	6.25
1-2	3	9.37	-	-	-	-	1	3.12	-	-	1	3.12
3-5	4	12.50	1	3.12	-	-	-	-	-	-	3	9.37
6-10	1	3.12	-	-	1	3.12	-	-	-	-	-	-
10-15	1	3.12	-	-	-	-	-	-	-	-	-	-

Table 3: Clinical features of bleeding disorders.

Clinical feature	Deficiency abnormality					
	VIII	IX	XIII	Platelet	I	VII
Subcutaneous hematoma	14	2	-	2	1	-
Hemarthrosis	12	3	1	-	-	1
Bleeding gums	12	2	2	5	-	1
Bleeding after dental extraction	6	1	1	1	1	1
Epistaxis	3	2	2	3	-	1
Purpura	-	-	-	1	-	-
Hematuria	1	-	1	-	-	1
Hematemesis	1	-	-	-	-	-
Intracranial bleed	1	-	1	-	-	-
Prolonged umbilical bleeding	-	-	1	-	1	-
Menorrhagia	-	-	-	1	-	-
Prolonged external bleeding	-	-	-	1	-	-
Prolonged post-operative bleeding	1	-	-	-	-	-
Asymptomatic	1	-	-	-	-	-

Clinical features

The commonest clinical manifestation was subcutaneous hematoma. 22 children complained of bleeding gums followed by spontaneous hemarthrosis (17 episodes). Bleeding after dental extraction was another common symptom. Other less common clinical features were epistaxis, haematuria and hematemesis. Prolonged bleeding after trauma was present only in 15 cases. Two children one with factor VIII deficiency and one with factor XIII deficiency presented with intracranial bleed. History of prolonged umbilical bleeding during neonatal period was present in one girl with factor XIII deficiency and one boy with fibrinogen deficiency. One girl with platelet disorder when questioned complained of menorrhagia (Table 3).

Amongst the clotting disorder the common joint to be involved was knee (10 patients) followed by ankle (3 patients) and then elbows (3 patients). Only one patient complained of shoulder joint involvement (Table 4).

Table 4: Joint-involvement in congenital clotting disorder.

Joint involved	Deficiency				
	VIII	IX	XIII	VII	Total
Total cases	**18**	**3**	**3**	**1**	
Knee	10	3	3	1	15
Elbow	3	1	0	1	5
Ankle	3	1	1	1	6
Shoulder	1	-	-	-	-

Long term complication of bleeding disorders

Out of 32 patients 10 children were found to have growth retardation. 21 patients had anemia. Six children had joint deformity. Two children one with factor VIII deficiency and one with factor XIII deficiency developed hemiplegia probably secondary to intracranial bleeding. One child was HIV positive and another Hepatitis B positive. One child with factor VIII deficiency had hydrocephalus. School absenteeism and school dropout was noticed in 4 children (Table 5).

Investigations

21 children (65.62%) were found to be anaemic with a Hb% of less than 10grams%. 13 were found to be severely anaemic (i.e.) Hb% of less than 8 grams% (40.62%). *Platelet count* was found to be normal in 28 patients. 6 patients with platelet disorders had decreased platelet count was with abnormal forms.

Clot retraction time was within normal limits in 28 patients. Poor clot retraction was found in 6 cases of platelet disorders.

Table 5: Long term complications in bleeding disorders.

Complication	Number	Percentage
Joint deformity	6	18
HIV infection	1	3
Hepatitis B	1	3
Hemiplegia	2	6
Hydrocephalus	1	3
Growth retardation	10	-
Anemia	21	65
School dropout and school absenteeism	4	12

Clotting time (CT)

10 out of 26 patients with clotting disorder had prolonged CT and a normal bleeding time. One patient with fibrinogen deficiency had both bleeding and clotting time prolonged. All the patients with platelet disorder had prolonged BT (bleeding time) and normal CT(clotting time).

Activated partial thromboplastin time (APTT)

All haemophilia A and B deficiency patients had prolonged APTT as compared to control except for one infant aged 5 months had normal APTT.

Prothrombin Time (PT)

PT was normal in patients with factor VIII and IX deficiency. A girl with factor VII deficiency had prolonged PT. one boy diagnosed as fibrinogen deficiency had both PT and APTT prolongation.

Thrombin generation test (TGT)

TGT was done for 11 patients. TGT alone as a diagnostic test was performed for 5 patients. TGT and mixing experiment was done for one child only. TGT and mixing experiment and factor assay was performed on one patient. TGT and factor assay was diagnostic in 4 patients.

Mixing experiment

Mixing experiment was done in 11 patients. Nine patients with factor VIII deficiency were confirmed by mixing experiment. In two cases of factor IX deficiency mixing experiment was able to detect the deficiency.

Factor assay

Factor assay was done for 13 cases. Out of these 7 cases were severe haemophilia and 6 cases of moderate haemophilia.

Factor VIII

– Less than 1% - (7 cases) severe haemophilia A.

– 1-5% - (3 cases) moderate haemophilia A.

Factor IX – 1-5% - (3 cases) moderate haemophilia B.

Platelet disorders

All the 6 cases of platelet disorders had normal clotting time with prolonged bleeding time with poor clot retraction. 2 patients with Bernaud Soulier syndrome had reduced platelets with giant forms. Platelets functions were abnormal with Ristocetin. 4 of the thrombasthenia cases had normal clotting time and prolonged bleeding time. 2 children had reduced platelets with giant forms and 2 patients had discrete distribution of platelets. Platelets function studies were done for all the six cases of platelet disorders. All of them had absent aggregation with ADP (adenosine diphosphate) and Ristocetin.

Fibrinogen assay was performed in one child which was less than 50mg% (normal level above 150mg %). One patient with factor VII deficiency had a factor VII level of less than 1%.

DISCUSSION

Amongst the hereditary bleeding disorders haemophilia is the commonest congenital haemostatic defect that comes to clinical attention in developing countries. It is universally prevalent, the incidence being 1 in 5000 male births[3.] The present study also follows the same pattern. Factor VIII deficiency was the commonest (18 out of 32) bleeding disorder, followed by factor IX (3 out of 32). Haemophilia B is reported to occur in 1in 30,000 live births.

Haemophilia is an X-linked recessive disorder more common in males. The sex distribution in this study is in conformity with the above generalized statement. All haemophilia patients (21 out of 32) were found to be of male sex. Factor XIII deficiency and factor VII deficiency being autosomal recessive disorder is equally prevalent in both sexes.[8] In the present study one female

had factor VIII deficiency and one female and two males sex were diagnosed to have factor XIII deficiency.

Platelet disorder being an autosomal recessive both males and females are equally affected. The present study also reflects male: female ratio to be 1:1. There was an isolated case of fibrinogen deficiency.

Family history was positive only in 17 out of 32 cases. It is possible to detect haemophilia carrier by pedigree analysis. But both pedigree data and phenotype assessment have their own limitation. Mild cases may go undetected in the family. The disease may skip generations. Females are usually less symptomatic. Hence a family history may not be obtained in all cases; mutation has been reported to be 5 fold higher in male germ cells compared to female germ cells especially in haemophilia A. So this can result in a proportion of 50-60% of sporadic cases in severe haemophilia A.

Age of onset of bleeding in majority of cases was less than 5 years (71.8%). 50% of the above had their first bleeding episode below one year of age. Of the above, 10 patients bled before 6 months of age. It is well known that the severity of bleeding depends on the level of factor. In cases with level less than 1% of the bleeding episode can occur even during neonatal period. One case of factor VIII deficiency and one case of factor XIII deficiency manifested with umbilical bleed during the first week of life.

Subcutaneous hematoma and bleeding gums were the commonest manifestations reported. Haemarthrosis was a predominant feature of factor VIII and IX deficiency and one patient with factor XIII deficiency. Two children presented with serious complication of intracranial bleed. Sibling screening of one patient showed a factor level of less than 1% but was asymptomatic. Platelet disorders presented predominantly with bleeding gums, epistaxis, purpura, menorrhagia and subcutaneous hematoma.

Isolated patient with fibrinogen deficiency presented with prolonged bleeding after dental extraction, subcutaneous hematoma, bleeding gums and muscle bleeds. The commonest joint to be involved in all haemophiliacs is knee followed by ankle as these two are weight bearing joints can be subjected to trivial trauma frequently. But in severe cases multiple joints are involved simultaneously. If these joint bleeds are not treated promptly it can lead on to destruction of bones, chronic synovial thickening, joint deformity, wasting of muscle around the joint and contractures. Haemophilia patient with musculoskeletal deformity forces a formidable therapeutic challenge.

Inadequately treated patient with bleeding disorder can present with anemia, (21 of 32 had mild to moderate anemia in the present study) which results in severe growth retardation. They also drop out from school frequently due to severe frequent episodes of bleeding, pain and functional disability. Untreated haemophilia patient develop permanent joint deformity which was also the case in the present study. Six out of 32 patient, had deformity. This could be prevented by specific factor administration very early during an acute bleed and adequate physiotherapy regularly. Two patients with intracranial bleed developed hemiplegia and one had hydrocephalus in addition. Two children unfortunately had HIV and hepatitis B positivity probably due to administration of unsafe blood products.

Gene therapy holds the key to permanent cure of these patients in the near future.[9]

Investigations

Bleeding and clotting time

Only 10 out of 26 patients had a prolonged clotting time and normal bleeding time. Thus it is obvious bleeding and clotting time cannot be used as a screening test to rule out conclusively a congenital bleeding disorder. Prolonged bleeding time is present in all platelet disorders and also in severe form of Von Willebrand's disease.

PT and APTT were performed for all the cases of factor VIII and IX deficiency. PT was found to be normal in all the above patients except in an infant who was less than 6 months of age. Factor VII deficiency is basically a disorder of intrinsic pathway manifested with prolongation of PT. PT time was found to be prolonged in fibrinogen deficiency and factor VII deficiency.

Partial thromboplastin time test is a sensitive and quick way of demonstrating defects of coagulation too small to lead to prolongation of whole clotting time. This test is useful in the detection of haemophilia A and B, but however will not distinguish between the two.[4]

Thromboplastin – generation test (TGT)

Main value of TGT is in the presumptive diagnosis of haemophilia. If plasma defect alone is found with normal PT haemophilia is the probable diagnosis. The test gives abnormal results in the presence of circulating anticoagulant and can be used in testing mixtures of patients and normal absorbed plasma samples. TGT is capable of demonstrating mild form of factor VIII and IX deficiency and hence factor assay is the gold standard for definite diagnosis.

Factor assay

In the present study 13 out of 32 patient where subjected to factor assay. Seven cases of factor VIII were detected to have severe form of factor VIII deficiency (factor level less than 1%) and 6 cases had moderate factor VIII deficiency with a factor level of 1-5%. 3 cases of factor IX deficiency had factor level of 1-5%. Factor seven deficiencies were also of severe nature with a factor level

of less than n 1%. Patient with hypofibrinogenemia was found to possess a level of less than 50mg%.

Though it is said that patient with severe factor deficiency tend to bleed frequently and spontaneously it is surprising to note one factor VIII deficiency patient with severe factor deficiency had not had even a single bleeding episode up to 5 years of age.

For a person with hemophilia, gene therapy would allow continuous synthesis of a normal protein to correct the deficiency in vivo by placing non-defective, normal functioning genes into his cells.[9]

Platelet function studies

All the platelet disorders cases were subjected to platelet disorders cases were subjected to platelet function studies and showed absent aggregation with ADP and Ristocetin. All these cases were symptomatic.

CONCLUSION

Spreading awareness regarding bleeding disorders along with prompt diagnosis, appropriate treatment and follow up and genetic counseling is essential to prevent morbidity due to congenital bleeding disorders in children.

Funding: No funding sources
Conflict of interest: None declared
Ethical approval: The study was approved by the Institutional Ethics Committee of the Obafemi Awolowo University Teaching Hospitals' complex (OAUTHC), Ile-Ife, Nigeria

REFERENCES

1. Shruthi N, Marwaha RK, Trehan A. Hemophilia: Clinical features and complications. Paediatrics Today. 2001;4(7);285-8.
2. Kelley LA. Alexis the Prince who had hemophilia. LA Kelly Communications. 2-4.
3. Control of hemophilia: WHO, Geneva 16-17; June 1997.
4. Dacie and Lewis Practical Hematology. Bain BJ, Bates E, Laffan MA. 11th edition. 2012.
5. Ganong's review of Medical Physiology. Barrett KE, Barman SM, Boitano S, Brooks HL. Tata McGraw-Hill, 24th edition. 568-569. 2009.
6. De-Gruchy's Clinical Hematology in Medical Practice. Firkin F, Chesterman C. Chapter 14. Wiley Ind Pvt Ltd. 5th edition. 1989.
7. Biggs R. Human blood coagulation and its disorder, Blackwell Scientific Publication, Oxford, 1962.
8. Sohail MT, Heijnen L. Comprehensive Haemophilia Care in Developing Countries. 2001. Montreal: World Federation of Hemophilia.
9. Jones P. The prevention of hemophilia: Carrier detection and prenatal diagnosis guidelines for the development of a National Programme for haemophilia W.H.O. 43-48. 1996.

Cite this article as: Kannan P, Anitha Mohan C. A clinico haematological study of inherited bleeding disorders in children. Int J Contemp Pediatr 2016;3:896-901.