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Original Research Article

Clinico-Haematological Study of Rare Bleeding Disorders- A 5 year Retrospective Study

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Abstract

Background: The clinical heterogeneity of Rare bleeding Disorders (RBDs) associated with their rarity is a significant barrier to enhancing their deeper knowledge. Diagnosis, classification and adequate treatment of these disorders has been hampered by the variable clinical presentation and difficulty in recognizing affected patients, difficulty in collecting longitudinal clinical data and limits of laboratory assays. The objective this study is to evaluate the distribution of RBDs amongst inherited bleeding disorders and approach to RBDswith clinical evaluation & lab diagnosis. ***Materials and methods:*** This is a Retrospective study of rare bleeding disorders obtained from the cases referred from Karnataka Haemophilia Society to the Haematology section of department of Pathology, JJM Medical College, Davangere from June 2006 to June 2011. ***Results:*** Out of the total of 400 patients of inherited bleeding disorders referred, 23 were diagnosed of RBDs which included 11 cases of factor XIII deficiency, 4 of Hypofibrinogenemia, 3 of Afibrinogenemia, one each of factor II,V,VII,XI deficiency. ***Conclusion:*** RBDs poses significant social problem in our country. Lab diagnosis of these disorders is complex but basic coagulation set up with high clinical suspicion can take up the challenge of diagnosing these disorders.

Keywords: Deficiency, Factor, Haemorrhage, Rare bleeding disorders (RBDs).

INTRODUCTION

Rare bleeding Disorders (RBDs), representing 3–5% of all inherited coagulation factor deficiencies, include the inherited deficiencies of fibrinogen, FII, FV, FV+FVIII, FVII, FX, FXI and FXIII, generally transmitted in both sexes in autosomal recessive manner [1].

The prevalence of homozygous or double homozygous forms in general population vary from 1:500.000 for FVII deficiency to 1 in 2.000.000 for prothrombin and FXIII deficiency [1].

Relative frequency varies among populations, being higher where consanguineous or endogamous marriages are common, with increased frequency of specific mutant genes [2-6].

RBDs are characterized by a wide variety of symptoms from mild to severe which can vary significantly from one disorder to another, and from one patient to another even when suffering from the same type of disorder [7].

The clinical heterogeneity of RBDs associated with their rarity is a significant barrier to enhancing their deeper knowledge. Diagnosis, classification and adequate treatment of these disorders has been hampered by the variable clinical presentation and difficulty in recognizing affected patients, difficulty in collecting longitudinal clinical data and limits of laboratory assays [7].

Wide spectrum of clinical symptoms vary from a mild to moderate bleeding tendency to potentially serious/ life threatening haemorrhages [8].

Clinical symptoms in severe RBDs (Table-1**)** [**9]**

Table-1: Clinical symptoms in severe RBDs

RBD	Main bleeding symptoms for severe deficiencies
Afibrinogenemia, hypo and dysfibrinogenemia	Common: Umbilical cord, Epistaxis, First-trimester abortion Less common: Skin, GI, Genito-urinary tract, CNS, Menorrhagia Uncommon: Musculoskeletal
Prothrombin deficiency	Common: Subcutaneous and muscle hematomas Prolonged post-injury Mucosal tract Hemarthrosis Menorrhagia Less common: Postoperative Uncommon: CNS, GI
FV deficiency	Common: Epistaxis, Menorrhagia, Skin, Mucosal tract Postoperative Less common: Umbilical cord, Hematomas, Hemarthrosis Rare: CNS, GI
Combined FV and FVIII deficiency	Common: Easy bruising ,Epistaxis, Gingival postoperative, Post-dental extraction, Post circumcision, Menorrhagia, Post partum Uncommon: Hemarthrosis, Umbilical cord Rare: CNS, GI
FVII deficiency	Common: Easy bruising, Epistaxis, Gum bleeding , Menorrhagia, After surgery Less common: Hemarthrosis, Hematoma, Hematuria CNS, GI
FX deficiency	Common:Umbilical cord, Epistaxis, Menorrhagia, Hemarthrosis, Hematomas, Post trauma, Postoperative Less common: CNS, GI, Hematuria
FXI deficiency	Common: Oral cavity, Postoperative Menorrhagia
FXIII deficiency	Common: Umbilical cord, CNS Ecchymosis, Subcutaneous, hematoma, Oral cavity After trauma ,Menorrhagia, Miscarriages and intraperitoneal Less common: Wound healing, Hemarthrosis, Muscle hematomas ,Epistaxis, GI, Postoperative

Laboratory Diagnosis

Laboratory diagnosis RBD laboratory diagnosis is initially investigated via coagulation screening tests including the APTT and PT**.** A prolonged APTT with a normal PT suggests FXI deficiency after exclusion of FVIII, FIX, and FXII deficiencies. The reverse pattern is typical of FVII deficiency, whereas the prolongation of both tests directs further analysis toward deficiencies of combined FV and FVIII, FX, FV, prothrombin, or fibrinogen. All coagulation tests depending on the formation of fibrin as the end point are necessary to evaluate fibrinogen deficiency; hence, beside the PT and APTT, the TT is performed [9]. An abnormal APTT is repeated on 50:50 mixtures of a known congenitally deficient plasma and the test plasma, or on 50:50 mixtures of aged (deficient in I, II ,V, VIII factors) adsorbed (deficient in I,VII,IX,X) plasma and test plasma until correction is obtained and the missing factor identified [10]. Abnormal screening coagulation tests are followed by mixing studies (50:50) to exclude an inhibitor. When mixing studies correct, specific factor assays are performed to identify the deficiency. Factor antigenic assays are essential for diagnosis of quantitative deficiencies of fibrinogen or FII to appropriately classify and treat patients with dysfibrinogenemia and dysprothrombinemia, both associated with an increased thrombotic risk. The screening clotting tests (PT, APTT, fibrinogen, platelet count, and bleeding time) are normal in FXIII deficiency (Table-2); diagnosis is established via specific assays [9].

Table-2: Laboratory diagnosis of RBDs

Deficiency	Tests
Fibrinogen	Afibrinogenemia: TT ↑↑, APTT ↑↑, PT ↑↑ Dys- and Hypodisfibrinogenemia: TT ↑, APTT ↑, PT ↑↑
Prothrombin	TT normal, APTT ↑, PT ↑
Factor V	TT normal, APTT ↑, PT ↑
Combined factor V and VIII	TT normal, APTT ↑, PT ↑
Factor VII	TT normal, APTT normal, PT ↑
Factor X	TT normal, APTT ↑, PT ↑
Factor XI	TT normal, APTT ↑, PT normal
Factor XIII	TT normal, APTT normal, PT normal Specific assays required

MATERIAL AND METHODS

- This is a Retrospective study of rare bleeding disorders obtained from the cases referred from Karnataka Haemophilia Society to the Haematology section of Department of Pathology, JJM Medical college, Davangere from June 2006 to June 2011
- Diagnosis was based on clinical history, physical examination and laboratory work up.
- Laboratory work up included intial screening with BT, CT, PT, APTT & TT. Abnormal samples were treated with aged and absorbed plasma and further mixing studies were done to rule out the presence of inhibitors. Clot solubility test was performed with 5M urea solution for samples with normal screening tests.
- Out of the total of 400 patients of inherited bleeding disorders referred 23 were diagnosed of RBDs

RESULTS

Age (Table-3)

Table-3: Age wise distribution of patients included in the present study

Age (yrs)	Total Number	Percentage
0-5	3	13.04%
6-10	9	39.13%
11-15	3	13.04%
`6-20	4	17.39%
21-26	3	13.04%
26-30	1	4.34%
Total	23	100%

Distribution of RBDs (Table-4)

Table-4: Distribution of RBDs

Diagnosis	Number of cases	Percentage
Factor XIII deficiency	11	47.82%
Hypofibrinogenemia	4	17.39%
Afibrinogenemia	3	13.04%
Dysfibrinogenemia	1	4.34%
Factor II deficiency	1	4.34%
Factor V deficiency	1	4.34%
Factor VII deficiency	1	4.34%
Factor XI deficiency	1	4.34%
Total	23	100%

Sex distribution: showed RBDs affecting predominantly males (73.91%) (Fig-1).

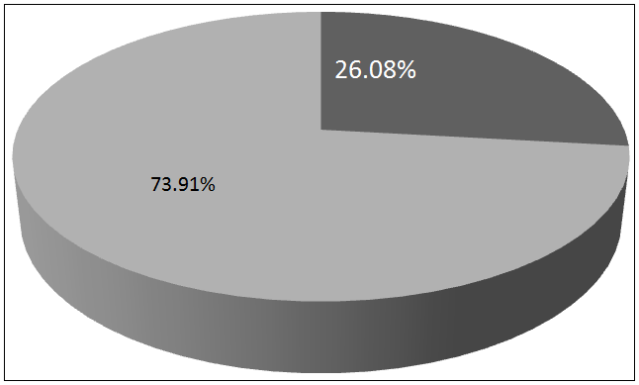

Fig-1: Sex Distribution

Consanguinity: RBDs more prevalent in consanguineous marriages (Table-5).

Table-5: Consanguinity

Consanguinity	Number of cases	Percentage
Present	19	82.60%
Absent	4	17.39%

RBDs
Factor XIII deficiency (Table-6)

Table-6: Presenting complaints in factor XIII deficiency

Presenting complaints	Number of cases	Percentage
Post traumatic(fig 1)	4	36.36%
Epistaxis	3	27.27%
Gum bleeding(fig 2)	2	18.18%
Surgical bleed	1	9.09%
Muscle hematoma	1	9.09%
Total	11	100%

- All patients had h/o umbilical stump bleeding at birth
- Haematological parameters, BT,CT,PT,APTT,TT were within normal range
- Clot solubility test done with 5M urea solution was positive in all cases

Fig-2: Post Traumatic Bleed

Fig-3: Gum Bleeding

Hypofibrinogenemia: 4 patients were diagnosed of hypofibrinogenemia (**Table-7).**

Table-7: Details of patients with Hypofibrinogenemia

Sl no	Age (yrs)/ Sex	Presenting complaints	CT in min	PT (control) In sec	APTT (control) In sec	TT (control) In sec	Fibrinogen assay
1	11 /F	Aching of lower limb & fever and cough with blood tinged sputum	>30	>180 (22)	>180 (32)	>180 (16)	<40mg/dl
2	12/F	Pain in the calf muscle, right side, cephal hematoma at the time of birth	>15	>120 (14.8)	>120 (34)	>120	<50mg/dl
3	10/M	h/o gum bleeding due to shedding of tooth, epistaxis on & off	20	54 (16)	119 (33)	>180 (20)	<50mg/dl
4	10/M	h/o recurrent gum bleeding & epistaxis	>30	109 (22)	98 (14)	>180 (16)	<50mg/dl

Correction studies: PT & APTT were corrected by normal & adsorbed plasma but not with aged serum

Afibrinogenemia: 3 patients were diagnosed of hypofibrinogenemia **(**Table-8).

Table-8: Details of patients with hypofibrinogenemia

Sl. No	Age/ sex	Presenting complaints	CT in min	PT (control) In sec	APTT (control) In sec	TT (control) In sec	Fibrinogen assay
1	22 /F	Traumatic bleed. h/o prolonged umbilical stump bleeding at birth+	>60	20.5 (12.5)	>180 (28)	>180 (18)	<10mg/dl
2	18/M	Episodes of prolonged mucocutaneous bleeds, h/o prolonged umbilical stump bleeding at birth+	>30	>180 (13.5)	>180 (29.7)	>180 (17.6)	<1.4mg/dl
3	3/M	Gum bleeding +, h/o prolonged umbilical stump bleeding at birth	>16	51 (14)	129 (32)	>180 (18)	<10mg/dl

Correction studies: PT & APTT were corrected by normal & adsorbed plasma but not with aged serum

Dysfibrinogenemia

- 11yrs/ Female,
- H/o recurrent gum bleeding. No past h/o umbilical stump bleeding at birth, h/o consanguinity +
- BT 2min, CT 3min 30sec
- PT 60sec. INR ratio 5.82, INR values 6.61.
- APTT >180 sec and TT 60 sec
- PT & APTT were corrected by normal & adsorbed plasma but not with aged serum
- Plasma fibrinogen level (Modified clauss) showed 350 mg/dl
- Liver function tests were normal

Factor II deficiency

- 23yrs/ Male
- H/o acute abdominal pain of 3days duration & with past h/o recurrent pain in the joints & muscles, h/o consanguinity is seen in parents.
- BT 3min, PT 70sec(16.1sec), APTT 44.3sec(33.4sec), TT 23.2(26.9sec)
- Both PT & APTT corrected with normal plasma & aged serum but not with adsorbed plasma
- FII- reduced, FX- normal

Factor V deficiency

- 10yrs/ Male
- h/o Recurrent gum bleeding & epistaxis , onset of symptoms since 5months of age when he presented with intracranial bleed, h/o consanguinity +
- PT- 44.6 sec(15.6 sec), APTT- 103.1 sec(36.3 sec), TT 14.6 sec(15.4 sec)
- PT & APTT corrected by normal & adsorbed plasma but not with aged serum.
- FVIII assay- 100%, FV < 1%

Factor VII deficiency

- 7months/ Male
- H/o bluish patches over cheeks and passing dark coloured stool. h/o intracranial bleed+. Consanguineous marriage of parents was seen.
- BT 2 min 30 sec, CT 4 min , PT prolonged (95 sec),INR ratio 6.10, INR value 7.44. APTT and TT were normal.
- Correction studies showed correction with normal plasma, aged serum but not corrected with adsorbed plasma. FVII assay was <1% and others FII – 69.7%, FX – 80%, FIX – 133.2%.

Factor XI deficiency

- 3½yrs / Male
- H/o easy bruisibility & prolonged bleeding after wounds from early infancy, No h/o consanguinity
- CT- upto 15min, APTT- 58.9 sec(33sec)
- APTT was corrected by normal ,adsorbed plasma & aged serum
- FXI- <1%

DISCUSSION

RBDs are common in pediatric age group with male preponderance well correlated with the literature (Table-9).

Table-9: Comparasion of age and sex preponderance

Study	Sajid R *et al*., (2010) [11]	Shanthala Devi AM *et al*., (1999) [12]	Shanthala Devi AM *et al*., (1999) [12]
Age Range	3 Years to 57 Years	-	7 months – 26 years
M:F Ratio	4:1	2:1	2.83:1

Consanguinity is being widely practiced & continues to be the main genetic basis constituting to 82.6% as observed in the study by Peyvandi *et al*., [8] & Sajid *et al*., [11]. Bleeding tendencies caused by inherited deficiencies of one or more coagulation factors are distributed worldwide. It is possible to diagnose most of these disorders by means of battery of simple laboratory tests and correlating with clinical presentation [13]. Predominant RBD, encountered in our study was FXIII deficiency, against the literature suggesting possibility of heterogeneity, gene mutations & polymorphisms. FXIII deficiency manifested with prolonged umbilical stump bleeding in accordance with the study by Anwar *et al*., [14], Schroeder [15] & Hsieh *et al*., [16]. Manifestations of fibrinogen deficiency vary widely depending on the concentration of

fibrinogen as observed in study by Acharya *et al*., [17] FXI & FV manifestations were comparable with commonly seen hemophiliacs however patients with FV deficiency did not show deeper bleeds. Patient with FVII deficiency experienced intracranial bleed in accordance with the study by Landau *et al*., [18]. The symptoms of afibrinogenemia started in neonatal period with all 3 cases presenting with umbilical cord bleeding in accordance with study by Acharya *et al*., [17].

CONCLUSION

- Since RBDs poses significant social problem in our country and very limited diagnostic and treatment facilities are available, we tried to study the clinico-haematological presentations & review the available literature.
- Lab diagnosis of these disorders is complex but basic coagulation set up with high clinical suspicion can take up the challenge of diagnosing these disorders.
- These patients are counselled and the options of treatment modalities were given for proper care. Affordable patients were referred to higher centre for further evaluation.
- RBD rarity limits indepth individual deficiency analysis and contributes to increased risk of misdiagnosis and poor and sometimes fatal consequences. Although many efforts have been made to address these gaps in RBD knowledge, further multinational collaborative efforts are required.

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