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An account of congenital rare bleeding disorders: a systematic study from a tertiary care centre in Eastern India

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ABSTRACT

Background: Rarity of rare bleeding disorders (RBDs) is attributed to very low incidence based on ethnicity, distribution and complexity of diagnostic tools. There is scarcity of data on RBDs from Eastern India. This study aims to understand the distribution of RBDs in this region for better patient care.

Methods: Retrospective study conducted on patients presented with symptoms/signs of bleeding from January 2018 to December 2019 (two years). Patients having bleeding manifestations from causes other than inherited coagulation disorders, IPDs, and vWD were included. Complete haemogram, peripheral blood smear, coagulation tests, vWD assay and platelet function tests were carried out.

Results: Out of 2415 patients, 1570 were included after exclusion of other diseases. Immune Thrombocytopenia (ITP) and Hemophilia being excluded, 40/1570 (2.5%) patients were found to have RBDs. Median age was 11.6 years (range, 1.25-40 years). Most common was IPDs (2.9%, n=19); Glanzmann thrombasthenia was commonest (1.5%, n=10). vWD was second (1.7%, n=11) in occurrence; vWD type-III was the commonest subtype (0.9%, n=6). ICDs comprised 1.5% (n=10) of all patients; congenital afibrinogenemia (0.6%, n=4) was most common. Other ICDs prevalent in this cohort included FVII, FV, FX and FXIII deficiencies. Most common presentations were ecchymoses or prolonged bleeding from cut injuries or menorrhagia.

Conclusions: RBDs may present in varied ways and are often difficult to diagnose correctly. Distribution of RBDs in this patient cohort differs from published literature from Western studies.

Keywords: Congenital coagulation disorders, Inherited platelet disorders, Rare bleeding disorders, Von willebrand disease

INTRODUCTION

Hemophilia A and B comprise 95-97% of patients with inherited coagulation disorders, while other rare bleeding disorders (RBDs) comprise remaining 3-5% of bleeding disorders; incidence of RBDs) range from 1 in 500,000 to 1 per million in general population.¹

RBDs include deficiencies of coagulation factors fibrinogen (FI), factor (F)II, FVII, FV, FX, combined FV

and FVIII, FXI and FXIII. These are mostly autosomal recessive conditions; some others like, FXI deficiency and dysfibrinogenemia may be autosomal dominant conditions.²

Prevalence of FVII deficiency, the most common factor deficiency, is one in 500,000, while the prevalence of FII or FXIII deficiencies, the rarest deficient factors, are one in 2-3 million population. The distribution of rarer bleeding conditions are not uniform over different

geographical areas, partly because it is not well studied in all cases. This is because specialized tests for the rarer factors are not available at all centers and also because sometimes the factor levels do not correlate with the extent of bleeding.⁴ Prevalence of vWD varies according to methodology used; varies according to the different types of vWD.⁵ Worldwide, vWD type-I is most common, but, Type III is most commonly reported in developing countries. The distribution of type II vWD varies according to the different subtypes.^{5,6}

The inherited platelet disorders are a collection of diseases, whose prevalence has not been accurately established due to their rarity. Platelet function disorders, including, Glanzmann's thrombasthenia and Bernard-Soulier syndrome are included in the rarer bleeding conditions. The more common inherited platelet disorders are the dense granule deficiency or defective thromboxane production disorders. Prevalence of hereditary type platelet disorders in India is suspected to be higher than in the Western countries.

There is a scarcity of published data from India, including West Bengal, regarding these RBDs. The aim of this study is to assess the distribution of these RBDs in the population of West Bengal, for better management of the same.

METHODS

A retrospective study conducted on patients attending the Hematology OPD at NRS Medical College from January 2018 to December 2019 (2 years).

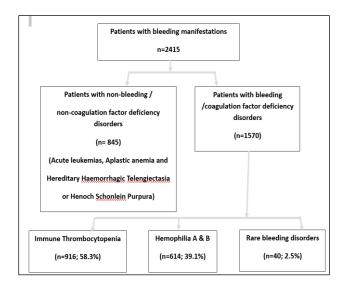


Figure 1: Consort diagram of patients included in the study (n=2415).

Irrespective of age, any patient who presented with history of bleeding or with complains of any bleeding manifestation (e.g. epistaxis, gum bleeding, menorrhagia, melaena, wet purpura, etc) was included in this analysis. Causes of haemorrhage from non-bleeding/non-

coagulation factor disorders, such as, acute leukemias, aplastic anemia and occasionally Hereditary Haemorrhagic Telengiectasia (HHT) or Henoch Schonlein Purpura (HSP) were excluded from the evaluation. The most common causes bleeding/coagulation factor disorders, such as, Immune Thrombocytopenia (ITP) and Hemophilia (A and B) were also excluded from the final analysis (Figure 1).

A complete hemogram, with peripheral blood smear examination and manual platelet count were carried out. Coagulation tests, including, Prothrombin time (PT), Activated Partial Thromboplastin time (APTT), Thrombin time (TT), Fibrinogen level were carried out. In addition, Clot solubility test (CST); assays for FV, FVII, FVIII, FIX levels; platelet aggregometry for platelet function tests; vWF assays, were also carried out to ascertain the diagnosis for individual patient.

RESULTS

Over a span of two years, 2415 patients attended the Hematology OPD with a history of bleeding with complains ranging from epistaxis, gum bleeding, menorrhagia, melaena, wet purpura, etc for variable duration. On analysis, Total 845 patients who had bleeding from causes (non-bleeding/non-coagulation factor disorders like, acute leukemia, aplastic anemia, myelodysplastic syndrome, HHT or HSP) other than factor deficiencies or platelet disorders were excluded from the evaluation. Out of remaining 1570 cases with bleeding symptoms; majority (58.3%, n=916) consisted of ITP followed by other bleeding disorders (41.7%, n= 654). And, out of these 654 cases, hemophilia comprised 93.9% (n=614/654) and RBDs comprised of 6.1% (n=40/654). Thus, RBDs comprised of 2.5% (n=40/1570)of the whole cohort (Figure 1). Here is a brief account of final evaluation on these 40 patients of RBDs.

The median age of patients with rare bleeding disorders was 11.6 years (range 1.25-40). There was a slight male (n=23/40) predominance in the cohort. Table 1 depicts the different types of RBDs in the present cohort.

Most patients were diagnosed with Platelet Function disorders (2.9%, n=19) of which Glanzmann thrombasthenia (GT) was the commonest (1.5%, n=10). vWD was second (1.7%, n=11) in occurrence in this cohort and vWD Type III was the commonest subtype (0.9%, n=6).

Rare coagulation factor deficiencies comprised 1.5% (n=10) of all patients. Of them, the most common factor deficiency was Congenital afibrinogenemia (0.6%, n=4). Other rare factor deficiencies which were found in this cohort include FVII, FV, FX and FXIII deficiencies.

Among the patients with rare coagulation factor deficiencies (n=10), the median age was 11.6 years (range 4.5-20), with male: female=1.5:1. Patients with

vWD (n=11) had a median age of 12.5 years (range 3.3-35) and male: female= 1.2:1. Platelet function disorders were seen in 19 patients, with a median age of 11 years (range 1.25-40), and male: female=1.4:1. The most

common presentation of these patients were bleeding manifestations, such as, ecchymoses or prolonged bleeding from cut injuries since childhood followed by menorrhagia (Figure 2).

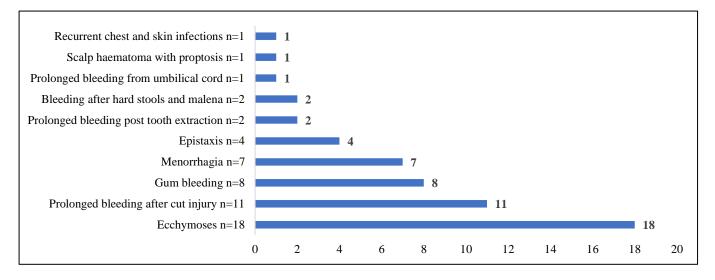


Figure 2: Distribution of patients with rare bleeding disorders, based on their presenting complaints (n=40). Many patients have more than one presenting symptoms.

Table 1: Distribution of patients with different rare bleeding disorders in this cohort, n=40 (total congenital bleeding disorders, n=654).

Type of bleeding disorder	Subtype	No. of patients (n)	Prevalence in percentage (n/654)
Platelet function disorder 2.9% (n=19/654)	Bernard soulier syndrome	4	0.6
	Glanzmann thrombasthenia	10	1.5
	Platelet granule disorder	3	0.5
	Wiscott aldrich syndrome	2	0.3
Coagulation factor deficiency 1.5% (n=10/654)	Congenital afibrinogenemia	4	0.6
	F VII deficiency	2	0.3
	F V deficiency	2	0.3
	F X deficiency	1	0.2
	F XIII deficiency	1	0.2
vWD Disease 1.7% (n=11/654)	vWD Type I	2	0.3
	vWD Type II	3	0.5
	vWD Type III	6	0.9

One patient of congenital afibrinogenemia had presented with subgaleal hematoma and proptosis as the presenting complaint at the age of 11 years. He had been asymptomatic since birth. Another patient with FXIII deficiency had prolonged bleeding from the umbilical cord.

DISCUSSION

The RBDs are 'rare' because of their limited prevalence, with a worldwide prevalence varying from 1-2/106 population worldwide; coagulation factor deficiencies

comprise up to 5% of all bleeding disorders.⁴ In a paper from Italy, Hemophilia A and B, and vWD together comprised 95-97% of bleeding deficiencies, and other rare coagulation disorders comprised the rest.⁷ Another study from France outlines the prevalence rates of inherited rare bleeding disorders to be between 1/500,000 and 1/2,000,000.⁸ The WFH data of 2016 estimates the prevalence of all inherited coagulation disorders to be 8%.⁹ This center is a tertiary care hospital a large population; many of them are referred from other hospitals. After ruling out all other causes of bleeding disorders as mentioned in Figure 1, the prevalence of rare

bleeding disorders was 6.1%. The major cause of bleeding disorders was the Hemophilia comprising 93.8% of RBDs.

The incidence of inherited bleeding disorders varies according to country and ethnicity. vWD is the most common inherited bleeding disorder in the United States and Europe, while platelet function defects are relatively rare. 10 A study from Egypt described platelet disorders to be most common (72.7%), including, ITP (74.8% of all platelet disorders); followed by inherited coagulation disorders (27.2% of all bleeding disorders). 11 Their study also highlighted that vWD was most common, followed by Hemophilia A and Hemophilia B. In a study conducted in AIIMS, India, it was found that Haemophilia A was most common 52.31%, and platelet function disorders came second 27.77%.6 In a study conducted in India from 1998-2002, the most common bleeding disorder was Hemophilia A 42.4%, followed by vWD 8.5%, Hemophilia B 5.1% and the other RBDs. FX deficiency was the most commonly detected 1.8%, followed by FXIII deficiency 0.8%, and the least common deficiencies were FVII deficiency (0.2%), FXI deficiency (0.2%) and FXII deficiency 0.1% (10). Data from an Egyptian study by Mokhtara et al, found Hemophilia to be commonest (84.5%), and of the rare coagulation deficiencies, commonest was FX deficiency (4.2%) followed by deficiencies of FVII (2.6%), Factor I (2.3%), FV (1.6%), combined factors deficiency (2.1%) and the rarest was FXIII deficiency (1.1%); unclassified coagulation disorders were found in 1.6%.11 In this observations, the most common deficiencies were the Hemophilia (93.9%), and among the rare bleeding disorders, the commonest were the Platelet function disorders (2.9%), followed by the vWD (1.7%) and least common were the rare coagulation factor deficiencies (1.5%). The commonest coagulation factor deficiency was found to be congenital afibrinogenemia (0.6%) and the rarest were FXIII or FX deficiencies (0.2%). In a study from Iran, 15.6% had rare bleeding disorders and the rest had Hemophilia or vWD and of the rare bleeding FV deficiency was commonest, afibrinogenemia was most uncommon.¹² According to the World Federation of Hemophilia, FXI deficiency with a prevalence of 37% and FVII deficiency with a prevalence of 23%, were the most common rare bleeding disorders. 13 Fibrinogen disorders and FV deficiencies were 10% each, FX deficiency was 9%, FXIII deficiency was 6%, combined FV + FVIII deficiency was 3% and the rarest was FII deficiency 2%. In another study by Shetty et al, most common RBD was FXIII deficiency.4 However, Sharma SK et al, had shown that, among RBDs, Factor X deficiency (43.28%) was the most common among North Indian population.¹⁴

In one study, the most common platelet function disorder was Isolated PF3 defect followed closely by the Glanzmann thrombasthenia.⁶ In this study too, the most common rare bleeding disorder (after Hemophilia and vWD) was FX deficiency, in contrast to this study, where

the most common rare coagulation disorder were Fibrinogen disorders. Mokhtara et al, showed that, similar to this findings, the most common platelet function disorder was Glanzmann thrombasthenia. The vWD type I is the commonest in Western countries, while vWD type III is common in countries like India or Iran. This is similar to the finding in this study, where Type III is the most common variety of vWD detected.

Coagulation factor defects were most common among males; this included Hemophilia. 10,12 Among females, vWD was the commonest. 10,15 There was a slight male predilection in this cohort as well. Gupta et al, have shown that patients with inherited coagulation disorders had variable age of onset varying from birth to 35 years, (median 7.2 years). 10 A study conducted in Iran, also had an age range of 1.25-91 years (mean age 25.8 years). 12 Most of our patients had presented between 1.25-40 years (median 11.6 years), quite similar to these studies. In another study, the rare bleeding disorders were detected in <1 year age group, while platelet disorders were detected between 6-14 years. In the same study, female sex was more common among platelet disorders, as opposed to rarer coagulation disorders.¹¹ A study conducted in India, noted that the age of diagnosis ranged from 3 months to 22 years.4 This study had a predominance of females. A study conducted in northern India, had 67 subjects, with a male predominance, median age 9years (range 2 months-54 years), and FX deficiency was most common. The rarest were FXI deficiency and combined FV and FVIII deficiency. 14

Hemarthroses (in Hemophilia) and mucocutaneous bleeding (in vWD) were the commonest presentations, menorrhagia was also common among patients with rare bleeding disorders. 10,12 Central nervous system bleeding was also noted in patients with FXIII deficiency. 10 Mucocutaneous bleeding, ecchymoses, epistaxis and gum bleeding were the commonest bleeding manifestations.⁴ Women with rare inherited bleeding disorders most commonly presented with menorrhagia. 15 It was reported that FXIII deficiency often lead to intracranial haemorrhage. 14 Patients with platelet function defects had a strong family history and the presentations were similar to those detected in this patients, like, prolonged bleeding after trauma, ecchymoses, epistaxis, gum bleeding or menorrhagia.⁶ As most of them have autosomal recessive inheritance, the distribution of different bleeding disorders vary depending on the region or race and the incidence increases in regions promoting consanguineous marriages.^{5,16} Furthermore, specialized tests are required for diagnosing the RBDs and are often not available or even if they are available, the tests are too expensive to be easily accessible, especially in countries with lower or lower-middle income. This leads to under-diagnosis of a lot of bleeding disorders and that further contributes to differential distribution of bleeding disorders apparently not matched with studies from other countries even from different region of a country also; this issue is very nicely discussed by Shetty et al.4 Another cause of differential distribution of the diseases is that often the levels of factors do not correlate with symptoms of factor deficiencies.⁴ Patients with milder deficiencies would often adjust and not attend a healthcare center in view of social or financial issues. They would often be missed.^{5,12} All the patients who were included in this study completed their diagnostic work-up. Greater number of patients will have to be followed up to understand the nature of these rare bleeding disorders and accurately characterize them for the benefit of the patients.

CONCLUSION

The rare bleeding disorders may present in many ways and are often difficult to diagnose correctly. It is important to pinpoint the exact diagnosis in order to accurately treat these patients, as the treatment modalities for RBDs are different from the other more common bleeding conditions, such as ITP or Hemophilia. A high index of suspicion is required to diagnose the RBDs. The present study found platelet function disorders were the most common, followed by vWD and finally the rare coagulation disorders.

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Ethical approval: The study was approved by the

Institutional Ethics Committee

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