A Clinico-Hematological Pattern of Bleeding Disorders in Children at a Tertiary Care Teaching Hospital

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ABSTRACT
Bleeding disorders (BDs) are quite uncommon, and most bleeding episodes commonly encounter in children as a result of local factors. However, the available literature is not enough to demonstrate the commonly encountered BDs among children. Hence, this study was intended to demonstrate the hematological pattern of BD’s over different age groups of children. In this prospective study, 100 patients of either gender, aged between 0 to 12 years attending the pediatric ward with bleeding manifestations were evaluated clinically to identify an underlying etiology by physical, familial and hematological examination. The data on demographics, family history, the onset of bleeding manifestations, laboratory findings, diagnosis with respective etiologies were collected, tabulated and interpreted. Out of 100 cases, 38% had acquired BDs, followed by platelet disorders (32%), inherited (26%) and vascular BDs (4%). Among acquired cases, disseminated intravascular coagulation (25/100) with hepatic impairment (40%) is the predominant cause. In inherited cases, von-Willebrand factor deficiency (18/100) was more predominant than factor VIII deficiency (12/100). School going children (6-9 years; 32%) and infants (21%) were the most affected age groups. Anemia (69%) and growth retardation (13%) were commonly observed complications. Acquired coagulopathies contribute a major portion of bleeding disorders in children. Infants and school-going children are at greater risk to develop coagulopathies. The understanding etiological cause is essential for accurate diagnosis and management in order to prevent morbidity associated with coagulopathies in children.

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INTRODUCTION
Bleeding disorders are characterized by abnormal or prolonged bleeding, due to disorders of platelets, blood vessels and coagulation factors which can be inherited or acquired. The prevalence of these coagulopathies varies depending on different age groups and most commonly seen in children as they are at greater risk for vitamin K deficiency (generally from birth to 6 months age), reduced procoagulant activity with a structural and functional difference of endothelium and platelets when compared to adults. In general, Vitamin K mediates the coagulation process by carboxylation of glutamate on coagulation factors (factor II, VII, IX and X). Dur-
ing infancy (especially the first month of life), its deficiency can lead to brain damage or death as there are no vitamin K reserves in the liver. (Knol et al., 2013; Philipp et al., 2005) Acquired coagulopathies are more common than hereditary disorders, but deficiency of clotting factor VIII and von willebrand factor is quite common with hereditary coagulopathies. (Rodeghiero and Castaman, 2001)

Earlier, before the advent of the various diagnostic and therapeutic measures, patients with BD’s will die due to uncontrollable massive bleeding. (Neunert et al., 2013) In recent times, advances in diagnostic and therapeutic measures have been evolved, but still, detection of the underlying cause lacks for prompt diagnosis and management. Hence, the diagnosis of the underlying disorder is of utmost importance with detailed physical, familial and hematological examinations. None of the studies has been established on the pattern of BD’s in children. Thus, this study was undertaken to study the hematological pattern of bleeding disorders among different age groups of children.

MATERIALS AND METHODS

Study design
This prospective observational study was carried out for a period of one year (Apr 2018 to Mar 2019) in the Dept. of Paediatrics after attaining ethical committee clearance and written informed consent from the parents.

Selection criteria
A total of 100 patients of either gender, aged between 0 months to 12 years, who presented with hemorrhagic manifestations (either a sign or symptom) were included in the study. The patients with medication history of heparin, coumadin and nonsteroidal anti-inflammatory drug therapy were exempted from the study.

Methodology
Data regarding age, sex, family history (regarding hematological disorders), age of onset and duration of bleeding disorders, hemorrhagic an infestation at the time of presentation were recorded in the pre-coded case report form. All the patients were evaluated clinically for coagulation and vascular disorders (by petechiae, deep dissecting hematomas, superficial ecchymoses, hemarthrosis and delayed bleeding). Later, basic hematological investigations including complete blood count, bleeding and clotting time (by dukes and Lee-White method respectively), clot retraction time, prothrombin time (PT) and activated partial thromboplastin time (aPTT) were measured in all patients. The patients who found with an abnormal PT underwent secondary investigations like fibrinogen assay, thrombin time, tourniquet test and vitamin K deficiency (assessed by PT, PTT and Liver function tests).

RESULTS

Demographics
Out of 100 patients presented with bleeding manifestations, males (54%) were slightly more than females (46%) with a ratio of 1.08:1. The minimum and maximum age of the patients were 1 day and 12 years, respectively, with the mean age of 5.6 ± 3.81 years. Out of 100, 22 patients had onset of bleeding, less than one year of age, whereas 21 patients had bleeding episodes during the first month of age. The school-going children were commonly affected with bleeding manifestations (6-9 years; 32%) followed by pre-school children (3-6 years; 21%) [Table 1].

Bleeding disorders
Majority of the patients were diagnosed with acquired coagulation disorders (38%) followed by platelet disorders (32%), congenital coagulation disorders (26%) and vascular disorders (4%). Out of all, 30% of patients have shown a family history of similar illness and suspected etiologies [Table 2]. All the bleeding disorders with respective etiologies are summarized in Table 2.

Hemorrhagic manifestations

Vascular disorders
All Henoch Scholein Purpura (HSP) patients presented with a purpuric rash on lower limbs and buttocks. Among HSP patients, two patients had an abnormal kidney function test, in which one patient had knee joint arthritis and one patient had a relapse after 6 months.

Platelet disorders
In idiopathic thrombocytopenic purpura (ITP); only one patient presented with petechiae, 12 patients with epistaxis and 6 patients complained of recurrence. In Acute leukaemia (ALL); Fever, bony pain, pallor, and abdominal distension were the predominant manifestations and 5 patients had hepatosplenomegaly. In aplastic anemia (AA); all the patients presented with nasal bleeding and bleeding spots all over the body, one patient had facial pigmentation, bifid thumbs and cafe-au-lait spots. A 6-year male child was presented with nasal bleeding and diagnosed as glanzmann’s thrombasthenia. Further, the patient was studied for platelet function defect and diagnosed as Glanzmann thrombasthenia. All enteric fever (2) cases presented with epistaxis during their illness.
Table 1: Age-wise distribution of patients by bleeding disorders

| Age group | VD | PD | CCD | ACD |
|-----------|----|----|-----|-----|
| 0 to 30 (d) | - | - | - | 21 |
| 1 to 12 (m) | - | - | 1 | - |
| 1 to 3 (y) | - | 3 | 4 | 1 |
| 3 to 6 (y) | 2 | 14 | 10 | 6 |
| 6 to 9 (y) | 2 | 9 | 5 | 1 |
| Total | 4 (4%) | 32 (32%) | 26 (26%) | 38 (38%) |

SD = standard deviation, n = no. of patients, VD = vascular disorder, PD = platelet disorder, CCD = Congenital coagulation disorder, ACD = Acquired coagulation disorder, d = days, m = months, y = years

**Congenital coagulation disorders**

All factor VIII deficiency patients with hemophilia A were a male child and 3 patients had a family history of similar illness. In contrast to von-willebrand's disease, 4 patients had a factor VIII deficiency and 9 patients had a family history of deficiency of the von-willebrand factor. Easy bruising, intramuscular and subcutaneous hematomas and epistaxis were the predominant bleeding manifestations seen in congenital coagulation disorders.

**Acquired coagulation disorders**

Disseminated intravascular coagulation is the most common among acquired coagulation disorder in which 18 patients had fibrinogen deficiency as well as abnormal liver function tests. In patients with vitamin K deficiency, 5 out of 8 had a family history of vitamin K deficiency [Table 3].

Out of 100 patients, 69% of patients had anemia, which might probably lead to growth retardation and school absenteeism. Two patients with DIC had intracranial bleeding and one child with hemophilia A had hydrocephalus. One patient had hepatitis B positive due to a positive family history of Hepatitis B virus [Table 4].

In all patients with platelet disorders, decreased CRT and prolonged BT was observed, whereas prolonged PT was observed in fibrinogen deficiency. All patients with factor VIII deficiency had abnormal aPTT with normal PT. One patient with both liver impairment and vitamin K deficiency had normal TT prolonged PT and aPTT [Table 5].

**DISCUSSION**

In this prospective study, we have studied 100 patients with bleeding manifestations where acquired coagulation disorders (38%) were the predominant coagulopathies than hereditary ones (26%). Among acquired cases, DIC (25%) is the predominant cause of bleeding. Majority of the DIC cases (72%) had abnormal liver function as hepatic damage may lead to the decrement of clotting factors, higher consumption viz. DIC and abnormal platelet function. (Mammen, 1992) A study conducted by Asthana et al. also reported a larger proportion of acquired cases (77.4%) with the leading cause of DIC (28.5%) and hepatic impairment (20.9%). (Asthana et al., 2009) Among the hereditary cases, factor VIII deficiency (hemophilia A and vWD) is the most common cause of bleeding. In the present study, all the hemophilia cases were male as it is an X-linked recessive coagulopathy, which is more common in male traits. Globally, the incidence of hemophilia A is 1 in 5000 male births. (Castaldo et al., 2007) Platelet disorders are autosomal recessive disorders in which both genders are equally affected. An almost similar pattern was observed for platelet disorder in the present study (Male, female ratio, 1:1). In vascular disorder HSP, 50% of the patients had renal impairment. Watson L et al. reported the incidence of renal impairment in 20% of HSP children. (Watson et al., 2012)

In acquired cases, 63% of cases had vitamin K deficiency and abnormal liver function, 21% had a family history of vitamin K deficiency as well. Most of the cases were observed during the first year of life and preschool age. During infancy, as there are no vitamin K reserves, a diet with low vitamin K during preschool and schooling age, and idiopathic liver impairment decreased the synthesis of vitamin K dependent clotting factors. In those cases, bleeding will be reversed by the administration of vitamin K. (Girolami et al., 2008) Prolonged PT and a PTT was observed in cases with vitamin K deficiency and liver impairment. Vitamin K deficiency decreases the activity of factors such as factor IX (evaluated by PTT) and factor VII (evaluated by PT) associated with intrinsic and extrinsic pathways, respectively. At earlier stages of deficiency, PT prolongs...
Table 2: Distribution of patients by bleeding disorders

|                          | Number (%) | ♂ (n; %) | ♀ (n; %) | FHx (n) | Abnormality detected (n) |
|--------------------------|------------|----------|----------|---------|-------------------------|
| **Vascular disorders**   |            |          |          |         |                         |
| Henoch Schönlein Purpura| 4 (4%)     | 2 (2%)   | 2 (2%)   | -       | KFT (2)                 |
| **Platelet disorders**   |            |          |          |         |                         |
| Idiopathic thrombocytopenic purpura | 16 (16%) | 10 (10%) | 6 (6%)   | HIV (3) | Thrombocytopenia (16)   |
| Acute Lymphoblastic Leukemia | 9 (9%)    | 4 (4%)   | 5 (5%)   | ALL (2) | Pancytopenia (9)        |
| Aplastic Anemia          | 4 (4%)     | 1 (1%)   | 3 (3%)   | HBV (1) | Pancytopenia (4)        |
| Thrombasthenia           | 1 (1%)     | 1 (1%)   | -        | GT (1)  | Thrombocytopenia (1)    |
| Enteric fever            | 2 (2%)     | 1 (1%)   | 1 (1%)   | -       | Thrombocytopenia (2)    |
| **Congenital coagulation disorders** |          |          |          |         |                         |
| Hemophilia A             | 8 (8%)     | 8 (8%)   | -        | H-A (3) | Factor VIII deficiency (8) |
| Von-Willebrand’s Disease | 18 (18%)  | 7 (9%)   | 11 (11%) | vWD (9) | Factor VIII deficiency (4) and vWF deficiency (18) |
| **Acquired coagulation disorders** |          |          |          |         |                         |
| Disseminated Intravascular Coagulation | 25 (25%) | 13 (13%) | 12 (12%) | VSD (1), PA (2) and AFE (1) | KFT (6), LFT (18) and fibrinogen deficiency (18) |
| Vitamin K Deficiency     | 8 (8%)     | 5 (5%)   | 3 (3%)   | VKD (5) |                         |
| Hemorrhagic disease of the newborn | 3 (3%)     | 2 (2%)   | 1 (1%)   | VKD (2) | VKD (3)                |
| Biliary atresia          | 2 (2%)     | -        | 2 (2%)   | -       | LFT+ VKD (1) and KFT (1) |
| **Total**                | 100        | 54 (54%) | 46 (46%) | 30 (30%) |                         |

♂ = male, ♀ = female, FHx = family history, ALL = acute lymphoblastic leukemia, HIV = human immunodeficiency virus, HBV = hepatitis B virus, GT = glanzmann’s thrombasthenia, H-A = haemophilia A, vWD = von willebrand disease, PA = placental abruption, VSD =ventral septal defect, AFE = amniotic fluid embolism, KFT = kidney function test, CSF = cerebrospinal fluid, LFT = liver function test and VKD = vitamin K deficiency

since factor VII has a short half-life among all vitamin K dependent coagulation factors, whereas, in advanced stages, PTT elevated, since factor IX has a longer half-life. (Silva et al., 2015)

In this study, 69% of cases presented with anemia, which might have led to growth retardation in 13% of cases. Due to severe bleeding and growth retardation, the drop out from the school was found to be 11%. Among DIC cases, 8% patients developed hemiplegia secondary to intracranial bleeding. According to a case series by Kawakami Y et al., four cases with DIC had intracranial hemorrhage. (Kawakami et al., 1990) In the present study, 18.7% of the ITP cases had an HIV related ITP as their mothers had an HIV ELISA positive. Five to ten percent of HIV infected patients develop ITP during their course of infection. (Shah, 2013)

Our study has a major limitation that the present study did not correlate bleeding manifestations with clotting factors and haematological investigations as well. Future studies are required to develop a correlation between manifestations and clotting factors.
Table 3: Hemorrhagic manifestations in bleeding disorders

| Clinical features                  | Bleeding Disorders (n) |
|------------------------------------|------------------------|
|                                    | VD | PD | CCD | ACD |
| Epistaxis                          | 0  | 7  | 6   | 5   |
| Easy bruising                      | 0  | 0  | 14  | 0   |
| Gum bleeding                       | 0  | 4  | 0   | 2   |
| Hematemesis                        | 0  | 0  | 0   | 6   |
| Hemarthrosis                       | 0  | 0  | 2   | 0   |
| Intramuscular and subcutaneous hematomas | 0  | 0  | 7   | 0   |
| Bleeding from injection sites      | 0  | 0  | 0   | 4   |
| Malena                             | 0  | 5  | 0   | 7   |
| Petechiae and Purpura              | 4  | 12 | 0   | 7   |
| Ecchymosis                         | 2  | 4  | 0   | 3   |
| Haematuria                         | 0  | 0  | 0   | 4   |

n = no. of patients, VD = vascular disorders, PD = platelet disorders, CCD = Congenital coagulation disorder, ACD = Acquired coagulation disorder

Table 4: Complications of bleeding disorders

| Complications            | Number (%) |
|--------------------------|------------|
| Anemia                   | 69 (69%)   |
| Joint deformity          | 8 (8%)     |
| Hemiplegia               | 3 (3%)     |
| Hepatitis B positive     | 1 (1%)     |
| Growth retardation       | 13 (13%)   |
| Hydrocephalus            | 2 (2%)     |
| School dropouts          | 11 (11%)   |

Table 5: Etiological distribution by laboratory findings

| Bleeding disorder                     | Number (%) | Laboratory finding                        |
|---------------------------------------|------------|-------------------------------------------|
| Factor VIII deficiency                | 12 (12%)   | ab aPTT, n PT                             |
| Vitamin K deficiency                  | 3 (3%)     | ab PT and aPTT                            |
| Fibrinogen deficiency and DIC         | 18 (18%)   | ↑ PT and aPTT with ↑ TT                   |
| Liver abnormality and vit K deficiency| 1 (1%)     | ↑ PT and aPTT with n TT                   |
| vWD and platelet disorders            | 1 (1%)     | ab platelet function test                 |
| ITP                                   | 16 (16%)   | ↓ platelets                               |
| Platelet disorders                    | 32 (32%)   | ↓ CRT, ↑ BT and n CT                      |

ab= normal, n = normal, PT = prothrombin time, aPTT = activated partial thromboplastin time, TT = Thrombin time, CRT = clot retraction time, BT = bleeding time, CT = clotting time, ↑ = prolonged and ↓ = decreased

for better etiological demonstration, prompt diagnosis as well.

CONCLUSION

Acquired coagulopathies contribute a major portion of bleeding disorders in children. Infants and school-going children are at greater risk to develop coagulopathies. The understanding etiological cause is essential for accurate diagnosis and management in order to prevent morbidity associated with coagulopathies in children.

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Conflict of Interest

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