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Short Report

Navigating the Diagnostic Enigma of Rare Inherited Disorders

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ABSTRACT

Inherited disorders of coagulation pathway often pose diagnostic challenges due to heterogenous clinical manifestation particularly when presenting at advanced age. They often go undiagnosed during childhood due to their atypical features, inadequate access to health care, lack of access to comprehensive laboratory workup, molecular testing and limited therapeutic options. In few women, features such as recurrent pregnancy loss, ectopic pregnancy, menorrhagia or infertility may be sole presentation in such rare conditions. Next-generation sequencing has enhanced the ability to accurately diagnose inherited bleeding and immune mediated disorders, enabling better genetic counselling and antenatal screening. We present a series of five cases with varied clinical profile, unexplained bleeding and adverse obstetric outcomes which caused diagnostic and management difficulties due to limited data in literature. This emphasizes the need to consider early application of molecular testing in such cases to improve diagnostic accuracy, guide appropriate management.

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INTRODUCTION

Recently, inherited disorders affecting haemostasis, platelet function, complement regulation, and immune homeostasis have been recognized as important but often overlooked contributors of adverse clinical outcomes as well as maternal morbidity globally.

In practice, only 30% patients referred for family or personal history as mild to moderate bleeding disorders (MBD) are diagnosed with known identifiable etiologies such as von Willebrand disease or platelet function disorder, rest of those classified as bleeding disorder of unknown cause (BDUC) as diagnosis of exclusion eventually manifest as peripartum/ post-partum hemorrhage or menorrhagia[1].Though the scientific and standardization committee of International society on thrombosis and haemostasis-bleeding assessment tool (ISTH-SSC BAT) represents the objective scoring system, overlapping phenotypes exist between BDUC and inherited platelet disorders[2].

Isolated or combined deficiency of rare clotting factors such as Factor (F) II, V, fibrinogen, VII, IX, X, XII, XIII are inherited as autosomal recessive disorders in majority, manifest with varied phenotype and cause diagnostic challenges. In patients suspected of BDUC and rare factor deficiencies, specialized testing such as light transmission aggregometry, platelet secretion assays/flow cytometry/electron microscopy, tests of fibrinolysis, thrombomodulin, rare clotting factor antigen and functional assays are not widely available in every centre. Target molecular testing may guide in identifying unknown bleeding phenotype, confirm genetic defects, plan for preventive strategies and management of such rare bleeding disorders (RBD). Additionally, definitive therapies for RBD and immune disorders including plasma derived/recombinant factors and targeted agents are still emerging in developing countries and have limited accessibility.

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Due to lack of uniform guidelines and consensus recommendations for treatment of such rare bleeding disorders (RBD), they remain undiagnosed till adulthood. Thromboelastography, thrombin generation potential and platelet function analyzer are not recommended for definitive diagnosis of such defects.[3]. We hereby discuss the clinical characteristics, diagnostic challenges and management limitations of five cases presented to tertiary care centre. They underscore the value of comprehensive genetic testing in atypical presentation, highlight the need for multidisciplinary evaluation, and discuss how molecular diagnosis transforms clinical management and risk assessment.

Case 1

A 35-year-old woman presented to the haematology outpatient department with a history of heavy menstrual bleeding since menarche, seven episodes of spontaneous miscarriages in first trimester including two ectopic pregnancies in the last ten years. Her previous evaluation for thrombophilia at another centre demonstrated prolonged activated partial thromboplastin time (APTT) of 48 seconds, heterozygosity for factor V leiden mutation. After repeated interrogation, prolonged muco-cutaneous bleeding following trivial injury was revealed. Despite extensive gynaecologic evaluation, etiology of menorrhagia remained unexplained. Bleeding score as per the ISTH-SSC bleeding score was calculated and described in Table 1. With the clinical suspicion of additional coagulation defect in view of recurrent pregnancy loss along with unexplained bleeding tendency, molecular testing using whole-exome sequencing was sent. It revealed compound heterozygous variant in the FXIIIA1 gene, consistent with inherited factor XIII deficiency. This rare autosomal recessive coagulation disorder is associated with recurrent miscarriages, increased bleeding, soft tissue hematoma and poor wound healing. As factor XIII plays a critical role in fibrin stabilization and maintenance of placental implantation, this explains the underlying clinical phenotype of the patient. Quantitative factor XIII antigen assay was not offered in our centre. She was advised peri-operative as well as on-demand factor XIII concentrate administration along with cryoprecipitate, fresh frozen plasma (FFP) and packed cell transfusion.

Case 2

A 26-year-old woman was evaluated for menorrhagia since menarche along with intermittent gum and skin bleeding outside. Complete hemogram showed thrombocytopenia with platelet count between 45-85 x 109/litre (L) on multiple occasions since 14 years of age. Screening coagulogram was normal. Bone marrow examination done outside demonstrated megakaryocytic thrombocytopenia. In view of clinical diagnosis of chronic immune thrombocytopenia, she was started on oral prednisolone after multiple episodes of intermittent bleeding manifestations since adolescence. As patient was cushingoid, had persistent menorrhagia, with moderate thrombocytopenia despite treatment with romiplostim and eltrombopag during presentation in our centre, inherited platelet function disorder such as Bernard-Soulier syndrome or von Willebrand disease type 2 was suspected. Clinical exome sequencing identified a pathogenic nonsense variant in the cluster of differentiation (CD)36 gene resulting in inherited platelet glycoprotein IV deficiency confirming the underlying clinical phenotype. Steroid and eltrombopag were stopped, continued on oral tranexamic acid during menstrual cycle. Her cushingoid features, menorrhagia and weight gain gradually declined. She was advised single-donor platelet concentrate transfusion during heavy menstrual cycles as well as during peri-operative period if required.

Case 3

A 28-year-old primi gravida with 32 weeks of gestation presented with excessive bleeding following tooth extraction. She did not give any significant past or family history of spontaneous or provoked bleeding episodes. Screening coagulogram revealed prothrombin time (PT) of 60 seconds, international normalized ratio of 5,activated partial thromboplastin time of 35 seconds, thrombin time (TT) of 14 seconds and fibrinogen of 285 milligram/decilitre(mg/dl). In suspicion of an inherited coagulation disorder, clinical exome sequencing was sent which revealed bile acid conjugation defect due to a homozygous variant of uncertain significance in the bile acid-CoA:amino acid N-acyltransferase (BAAT) gene. This is associated with the likelihood of fat-soluble deficiency leading to vitamin K deficiency and hence prolonged prothrombin time. She was being treated with intravenous vitamin K administration and FFP transfusion during bleeding episodes as well as in peri-partum for achieving hemostasis.

Case 4

A 27-year-old woman presented with history of recurrent skin and soft-tissue infections since one year of age. She developed multiple episodes of skin and soft issue infections following intramuscular injections for vaccinations as well as following thyroglossal cyst excision at seven years of age. Laboratory evaluation demonstrated persistent leucocytosis with elevated white cell count, raised inflammatory markers such as C-reactive protein, erythrocyte sedimentation rate (ESR), fibrinogen and serum ferritin. Her obstetric history was significant with two episodes of spontaneous first trimester miscarriages at eight weeks of gestation. Owing to the early age of onset of recurrent infections and pregnancy loss, an inherited immune dysregulation/deficiency was suspected. Clinical exome sequencing demonstrated a homozygous missense variant in the OTULIN gene, which is associated with autoinflammatory panniculitis and dermatosis syndrome due to dysregulation of the NF-κB inflammatory pathway. Short course of steroid was administered during episodes of aseptic cutaneous inflammation and panniculitis episodes. She was counselled for recombinant interferon (IFN) alfa-2b or interleukin-1 inhibitor (anakinra)as well as tumour necrosis factor (TNF) inhibitor based treatment during clinical attack based on reported cases in literature.

Case 5

A 17-year-old girl born out of non-consanguineous marriage presented with recurrent, intermittent episodes of painless swelling involving the face, upper airways and extremities since 3 years of age. Laboratory evaluation revealed absolute eosinophil count (AEC) of 0.51 x 109/L, serum immunoglobulin level (Ig)E of 336.8 International units/litre (IU/L) (Normal 1.31- 165.3 IU/L), serum complement(C)4 level of 6 milligam per decilitre (mg/dl) (normal 14-48 mg/dl), C3 level of 132 mg/dl (normal 88-201 mg/dl) and decreased C1 esterase inhibitor level of 0.07 mg/dl (normal 15-35 mg/dl) raising clinical suspicion of hereditary angioedema. Whole-exome sequencing confirmed the diagnosis as hereditary angioedema type 1 due to heterozygous pathogenic variant in the SERPING1 gene and low C1 esterase inhibitor level. At present patient is being managed with daily danazol. Oral tranexamic acid, FFP transfusion and subcutaneous adrenaline administration were advised during acute attacks.

Table 1 shows clinical and management details of individual cases

Factors	Case 1	Case 2	Case 3	Case 4	Case 5
Age	35 years	27 years	28 years	27 years	17 years
Gender	Female	Female	Female	Female	Female
Clinical history	Recurrent spontaneous miscarriages, prolonged APTT	Chronic menorrhagia, megakaryocytic thrombocytopenia, traumatic bleeding	Prolonged bleeding after tooth extraction, prolonged PT/INR	Recurrent skin and soft-tissue infections, leucocytosis, early pregnancy loss	Recurrent angioedema,low-C4,low C1 esterase inhibitor

Duration of symptoms	10 years	10 years	2 months	Since infancy	14 years
Consanguinity	No	No	No	No	No
ISTH-BAT score	6 points	--	4 points	--	--
Laboratory investigation	Prolonged APTT, factor V leiden mutation heterozygous	Normal PT, APTT and fibrinogen,, megakaryocytic thrombocytopenia on bone marrow	PT- 60 seconds, INR- 5	Total count between 16 to 22 x 109/L, with 5% lymphocytes (absolute T-cell lymphopenia), normal NBT burst cells: 98% (control 98%)	AEC-0.51 x 109/L, C4-6 mg/dl, C1 esterase inhibitor-0.07mg/dl, normal C3 level.
Working Diagnosis	Inherited coagulation factor deficiency and thrombophilia	Steroid refractory ITP	Inherited bleeding disorder ? Factor VII deficiency	Leukocyte adhesion deficiency or other primary immunodeficiency disorder	Hereditary angioedema
Molecular identification of transcript by sequencing	FXIIIA1	CD36	BAAT	OTULIN	SERPING1
Variant	c.1226G>A and c.232 C>T	c.971C>G	c.1174G>A	c.971C>T	c.550G>A
Variant Type	Missense	Nonsense	--	Missense	Missense
Consequence (HGVSp)	p.Arg409Gln, p.Arg78Cys				
	p.Ser324Ter	p.Ala394Thr	p.Pro324Leu	p.Gly184Arg	
Location	Exon 10 and exon 3	Exon 10	---	Exon 7	Exon 3
Zygosity	Compound heterozygous	Heterozygous	Homozygous	Homozygous	Heterozygous
Inheritance	Autosomal recessive	Autosomal recessive	Autosomal recessive	Autosomal recessive	Autosomal dominant
Variant Significance	Pathogenic	Pathogenic	Uncertain significance	Pathogenic	Pathogenic
Final Diagnosis	Congenital Factor XIII A subunit deficiency	Inherited Platelet function disorder due to CD36 glycoprotein deficiency	Bile acid conjugation defect	OTULIN-related Auto-inflammatory Syndrome (ORAS)	Hereditary Angioedema Type I (SERPING1-related)
Management	Recombinant factor XIII concentrate, cryoprecipitate and FFP transfusion.	Platelet concentrate, Tranexamic acid	Vitamin K, FFP transfusion.	Recombinant IFN alfa-2b or TNF inhibitor based treatment.	Danazol, tranexamic acid, FFP transfusion

Foot note: ISTH-SSC- The scientific and Standardization committee of International society on thrombosis and haemostasis, BAT-bleeding assessment tool, PT- prothrombin time, APTT- activated partial thromboplastin time, INR - international normalized ratio, AEC- absolute eosinophil count, ITP- immune thrombocytopenia, NBT- nitroblue tetrazolium test, FFP- fresh frozen plasma, c-coding DNA reference sequence, HGVSp- Human genome variation society

DISCUSSION

Factor XIII deficiency is one of the commonest cause of recurrent, prolonged umbilical stump, subcutaneous and muscle bleeding, spontaneous and intracranial haemorrhages in early neonatal period particularly when FXIII level is less than 3%. Though normal FXIII level is between 15-220%, maintainance of plasma FXIII activity level between 2-5% is adequate for normal hemostasis. During pregnancy, FXIII A and B subunit show dynamic variation as compared to other coagulation factors. FXIII A subunit decreases with the number of gestation particularly to 85% between 9 to 12 weeks whereas B subunit increases with gestation as similar to other factors[4]. Also, FXIII A subunit is necessary for the continuation of pregnancy. This reasonably elucidates the clinical presentation of recurrent early pregnant losses in the index case. Various published data in pregnancy recommends maintaining FXIII activity level above 10% prior to labour to mitigate early pregnancy losses and recurrent miscarriages as well as level above 20-30% in peripartum period to avoid hemorrhagic complications[5]. Though plasma derived (pd) FXIII products administered at dose of 10- 26 IU/kg every 7 days demonstrate reasonable efficacy and safety, occasional reports of pathogen contamination and low concentrate of FXIII in pdFXIII favour recombinant FXIII concentrate which has 13 times higher FXIII. It was first launched in 2015 in Japan, approved at dose of 35 IU/kg every 3 to 4 weeks to maintain the trough geometric mean FXIII activity level of 0.16 IU/ml[6].

Absence of CD36 glycoprotein expression on both monocyte and platelet is classified as type I defect whereas type II is CD36 deficiency only on platelet surface [7]. This can notably alter platelet reactivity and provoke anti CD36 antibodies during transfusion and pregnancy leading to life threatening complications such as severe anaemia, neonatal thrombocytopenia and recurrent foetal hydrops [8]. Though menorrhagia was the predominant clinical feature in our case, patient also had one episode of spontaneous miscarriage at seven weeks of gestation along with infertility. As current knowledge on association between infertility and CD36 deficiency is limited, future studies may evoke novel data impairing implantation in this disorder.

The final step in hepatic bile acid synthesis involving glycine and taurine conjugation facilitates lipid absorption through high intraluminal micellar production. Manifestations due to genetic defects interfering with bile acid amidation range from neonatal idiopathic cholestasis to unexplained fat soluble vitamin deficiency, prolonged prothrombin time, growth failure and mild to severe hepatic dysfunction[9]. Though defect in bile acid-CoA:amino acid N-acyltransferase (BAAT) is a familial hypercholanemia-3, typically present in childhood with elevated liver enzymes, unconjugated bile acids in blood and urine, vitamin K-dependent clotting factor deficiency presenting following tooth extraction was an uncommon presentation in the index case.

Otulin deficiency is characterised by excessive ubiquitylation and auto-inflammation resulting from altered nuclear factor κB pathway and reported only in ten cases in literature so far[10]. Our patient exhibited classical features as reported in other cases such as recurrent fever, panniculitis, diarrhoea and sterile abscess involving skin and lung [11]. Anakinra, interferon alfa 2b are reserved for severe episodes and short course of steroid was administered during mild attacks in our case.

Hereditary angioedema is an unpredictable, debilitating, life threatening condition characterized by increased vascular permeability due to excess bradykinin production resulting from plasma kallikrein dysregulation. Following administration of attenuated androgen, severity and frequency of facial and laryngeal oedema has reduced in our case. Since index case was a young adolescent female, concern remain on duration of androgen treatment, long term safety and issues regarding resurgence and worsening of existing oedema following C4 excess during FFP administration and limited treatment options. Prophylactic plasma derived C1 esterase inhibitor mitigated the attack rate at the dose of 300 mg subcutaneously every two weeks in nearly 40% of type 1 patients [12]. Recent literature shows elevated levels of plasma vascular endothelial growth factor (VEGF) correlated with worse disease control, increased severity, enhanced frequency of angioedema attacks[13].

CONCLUSION

Our experience illustrates the diverse clinical spectrum of rare inherited haematological disorders, their potential to remain unrecognized until adulthood, overlap with more common acquired disorders resulting in delayed diagnosis. This reiterates that genetic sequencing serves as a valuable tool when conventional clinical, laboratory evaluation is inconclusive, extensive coagulation assays are unavailable to enable precise molecular diagnosis, appropriate disease-specific management and facilitate personalized management. Multidisciplinary approach, early enrolment in clinical trials or multi-centric studies incorporating holistic diagnostic/treatment strategies enhance outcome, avoid treatment failure, develop future recommendations as well as strengthen nationwide database.

COMPLIANCE WITH ETHICAL STANDARDS

Availability of data and materials All data were collected from hospital electronic medical records and patient case files. Case series was prepared by collecting individual patient data, hence patient identity or personal information was not shared. Informed consent was obtained from all cases.

Conflict Of Interest

The authors declare no conflicts of interest.

Research involving Human Participants

Informed Consent was obtained from all cases.

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AUTHOR CONTRIBUTION

All authors contributed to patient care, diagnostic approach and management. MV and MC prepared the manuscript. All authors revised and approved the manuscript.

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