Case Series

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Multiple Coagulation Factor Deficiency: A Series of Eight Cases

Pathology Section

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ABSTRACT

Multiple Coagulation Factor Deficiency (MCFD) is an uncommon haematological disorder characterised by simultaneous deficiency of multiple clotting factors, which leads to an increased risk of bleeding and compromised haemostasis. The present series aimed to provide a comprehensive analysis of MCFD, shedding light on its aetiology, clinical manifestations, and potential therapeutic interventions in a case-by-case manner, highlighting the individualised treatment options that are needed for many of these cases. A prospective combined clinical and laboratory study was performed on all patients who presented with bleeding tendencies and were subsequently diagnosed with MCFD. Clinical records and laboratory data of all these patients were reviewed to identify commonalities and variations among affected individuals. Haematological assays were performed to quantify the extent of coagulation factor deficiencies. The present series identified a diverse cohort of eight individuals (2 females and 6 males) with MCFD, showcasing variability in age of onset, severity of symptoms, and potential underlying genetic mutations. Clotting factor assays revealed deficiencies of Factor V and Factor VIII (F5F8D), Vitamin K-dependent clotting factor deficiency, and failure of synthesis of clotting factors of hepatic origin. Clinically, patients presented with a spectrum of bleeding phenotypes, ranging from mild to severe, requiring tailored therapeutic strategies. The present series provides an overview of some of the presentations of MCFD, emphasising the need for a multidisciplinary approach in its diagnosis and management. Clinicians should be vigilant in recognising the varied clinical presentations of MCFD and consider genetic testing for precise diagnosis and management.

Keywords: Clotting disorder, Factor V, Factor VIII, Multiple factor deficiency, Vitamin K

INTRODUCTION

Multiple Coagulation Factor Deficiency (MCFD), both inherited and acquired, is a rare and intricate haematological disorder denoted by simultaneous deficiency of multiple clotting factors essential for proper coagulation function. Unlike more common single-factor deficiencies, MCFD represents a unique confluence of deficiencies in Factors II, V, VII, IX, X, and occasionally others, creating a complex clinical scenario that demands a nuanced understanding. Multiple factor deficiencies can be either familial or acquired and are further divided into two types: the first represents a simultaneous occurrence of more than one single-factor hereditary state, while the second is a single inheritable disorder associated with a deficiency of more than two factors [1]. Acquired causes, on the other hand, need to be investigated and treated appropriately. Understanding MCFD is crucial for optimising diagnostic strategies, tailoring therapeutic interventions, and ultimately improving patient outcomes [2].

CASE SERIES

Case 1

An 18-year-old female patient presented with recurrent mucosal bleeds since childhood, as well as prolonged bleeding following a tooth extraction 8 years ago. Her brother was diagnosed with haemophilia A. Her parents also revealed that she was easily bruised after minor trauma. Laboratory investigations showed prolonged clotting time as well as depleted levels of factor V and VIII, and a combined factor V and VIII deficiency was suspected. The patient was started on Desmopressin {1-deamino-8-D-arginine vasopressin (DDAVP)} and factor VIII concentrates and showed a satisfactory response to treatment. She is doing well and was advised regarding the nature of the disease.

Case 2

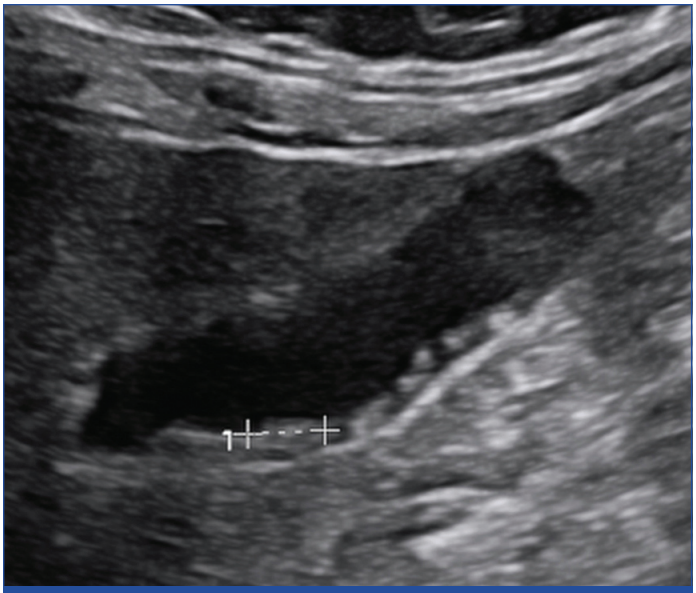
A 47-year-old male presented with swelling in the knee joints following minor trauma one week ago. He also revealed that he had similar complaints of epistaxis and joint bleeds for many years, which were symptomatically managed in a local nursing home. No significant family history was noted. Complete blood count showed thrombocytopenia (Platelet count-27,000/cumm). Coagulation screen revealed reduced levels of factors V (9.4%) and VIII (22.2%). He was advised prophylactic DDAVP as well as Fresh Frozen Plasma (FFP). Repeat coagulation screen showed correction of FVIII values (57.3%), while factor V remained slightly deranged (43.4%). The patient is currently asymptomatic and responded well to the treatment.

Case 3

An 11-year-old male patient complained of bloating and passing bulky stools, which were observed to float, aggravated by eating heavy meals since three months. He also complained of intermittently present over three years and ecchymotic patches over the anterior abdomen, measuring 4 cm in greatest dimension, which had developed six months ago. The coagulation profile showed low levels of factors II (15.5), VII (<5%), IX (34.3%), and X (14.6%). An ultrasound of the abdomen revealed cholecystitis with numerous gallstones [Table/Fig-1], which, in turn, had resulted in lipid malabsorption and subsequently Vitamin K malabsorption. He underwent cholecystectomy for the same, following which he was administered 10 mg of Vitamin K. He responded well to the treatment and procedure, showing complete remission of symptoms after four weeks, while the ecchymotic patches resolved after three days.

Case 4

A 59-year-old female complains of petechial spots and bruises over her chest since one month and a single ecchymotic patch over her lower back for five days. Past history revealed a high-grade fever associated with chills and rigours for three weeks, which was relieved on taking over-the-counter medications. She was then referred to a hospital due to the persistence of symptoms and was diagnosed with septicaemia. Blood culture was performed which was positive for *Klebsiella sp.* Following her current admission, complete blood



[Table/Fig-1]: Ultrasonography (USG) abdomen showing numerous stones in the gallbladder, largest measuring 1 cm in greatest dimension (white crosses).

counts revealed no abnormalities, while the coagulation screen depicted reduced levels of factors II (15.7%), VII (21.4%), IX (8.5%), and X (9.5%). Repeat blood cultures showed no growth. Vitamin K was administered, resulted in the resolution of her symptoms.

Case 5

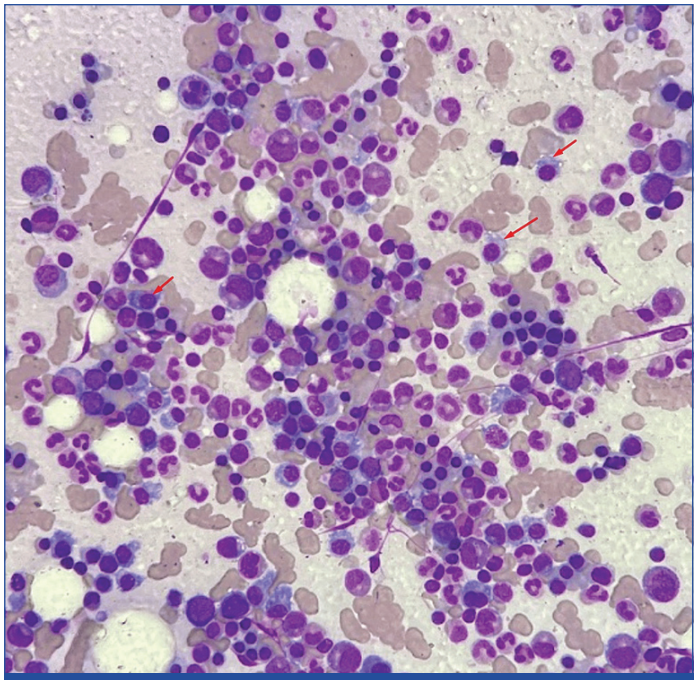
A 47-year-old male patient presents with sharp pain over the right hip joint since one week, which aggravates on walking and subsides with Non Steroidal Anti-inflammatory Drugs (NSAIDs), along with numerous reddish patches on his right thigh for one year. He had also taken various alternative medications of unknown brands to prevent Coronavirus Disease-2019 (COVID-19). Past history also revealed a fractured neck of the right femur, for which a bipolar prosthetic implant was inserted. Following this procedure, he was lost to follow-up and presented with his current complaints. Local examination revealed a few ecchymotic patches on the right thigh, with the largest measuring 5 x 4 cm. The right hip joint was swollen but non tender. The coagulation screen revealed deficiencies in factors II (24.6%), VII (<5%), IX (7.9%), and X (23.3%). He was advised against the use of NSAIDs without medical supervision and was administered Vitamin K (10 mg). The patient responded well to the treatment, and his coagulation parameters normalised after three days.

Case 6

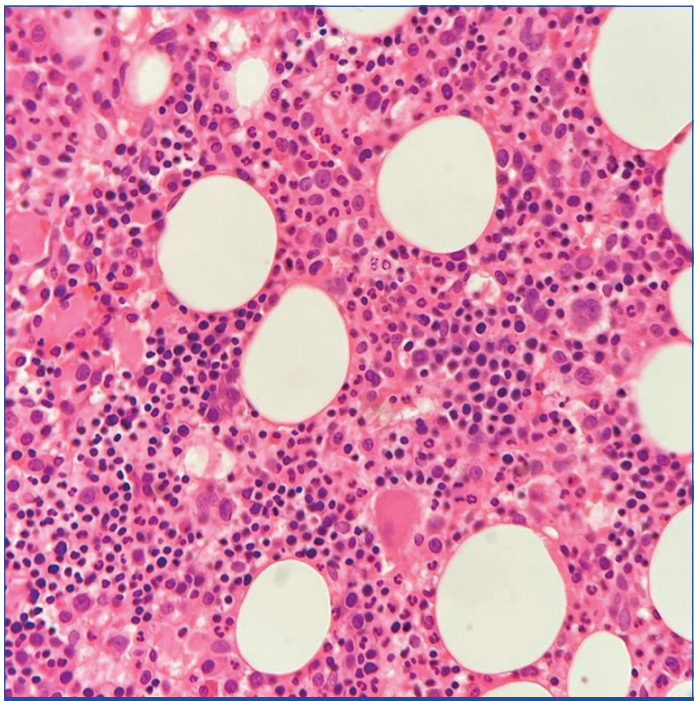
A 63-year-old male presented with epistaxis, haematuria, and melena for the past six months and had undergone previous surgeries without blood transfusion. The coagulation screen revealed reduced levels of factor V (29.5%) and X (35.8%). Bone marrow aspirate revealed the presence of numerous plasma cells (72%), while serum electrophoresis showed an M band of 1.9 g/dL, consistent with a diagnosis of multiple myeloma, suggested a possibility of myeloma-induced clotting factor deficiency due to excess light chain production. Bony lytic lesions were also noted in the lumbar spine on Computed Tomography (CT) abdomen. A bone marrow biopsy and aspirate were performed, as seen in [Table/Fig-2,3]. Increased plasma cells, plasmablasts, and binucleate forms were noted. He was initiated on the CyBor-D chemotherapy regimen and was followed-up with coagulation profiles and serum free light chain assay for six months. After three months, there was no detectable M band, and his symptoms were in remission.

Case 7

An 18-year-old male patient presented with ecchymosis over the back and shoulder for one year, along with chest pain and palpitations on strenuous exercise since five years. His Electrocardiogram (ECG) was unremarkable, while the echocardiogram showed left ventricular



[Table/Fig-2]: High power (40x) image of bone marrow aspirate depicting numerous plasma cells (red arrows). (May-Grünwald Giemsa (MGG) stain)



[Table/Fig-3]: High power (40x) image of bone marrow biopsy showing scattered plasma cells. Haematoxylin and Eosin (H&E)

outflow tract obstruction in the form of Aortic Stenosis (AS). Haematological evaluation, which included a coagulation screen, showed reduced levels of von Willebrand factor (vWF) (16.4%) and factor XI (23.3%). These features were suggestive of Heyde syndrome, due to the presence of acquired von Willebrand syndrome and AS. He was treated with DDAVP and planned for balloon valvuloplasty. He withstood the surgery well and is currently on prophylactic DDAVP. He was also advised against taking part in contact sports.

Case 8

A 26-year-old male patient complained of prolonged bleeding from a skin tag, along with persistent thrombocytopenia for six months (Platelet count- 50,000/µL), as tested at another centre. The coagulation panel revealed depletion of all clotting factors except factor VIII and vWF, both of which have an extrahepatic site of synthesis. Factor VIII was elevated in this case (FVIII- 158.1%). Further investigations also showed deranged liver function tests. An

ultrasound of the abdomen demonstrated moderate splenomegaly and cirrhosis of the liver. He was administered three units (750 mL) of FFP, which showed a slight elevation in the deficient factor levels (Factor II- 46.2%, Factor V- 53.6%, Factor VII- 57.4%, Factor IX- 42.3%, Factor X- 58.5%, Factor XI- 48.7%, Factor XII- 46.5%), and was stable on subsequent follow-up.

The eight cases are summarised in the table below with salient presenting features [Table/Fig-4]. A coagulation panel and bleeding work-up were done for all these cases, and the laboratory findings of each patient are summarised in [Table/Fig-5]. The individual details and relevant findings of each of these cases are further elucidated below.

Variables	Case 1	Case 2	Case 3	Case 4	Case 5	Case 6	Case 7	Case 8
Age (Years)	18	47	11	59	47	63	18	26
Sex	Female	Male	Male	Female	Male	Male	Male	Male
Bleeding Assessment Tool (BAT) score	8	7	6	7	8	6	7	7
Presenting complaints	Bleeding episodes since childhood	Bleeding episodes since childhood	Epistaxis, Haematoma	Ecchymosis	Ecchymosis, Haematuria	Ecchymosis, Haematuria, Melena	Ecchymosis	Prolonged bleeding from a small skin tag
Previous history	Brother diagnosed with haemophilia	No significant history	Cholelithiasis, fat globules in stool	Sepsis - Klebsiella	Implant for femur fracture	Previous surgeries without transfusion	Ventricular outflow obstruction	Persistent thrombocytopenia for 6 months
Treatment	DDAVP and FVIII concentrates	DDAVP and fresh frozen plasma	Inj. vitamin K (10 mg) and repeat coagulation screen, revealing correction in deficient factor levels.			CyBor-D (Cyclophosphamide, Bortezomib, Dexamethasone)	DDAVP and aortic valvuloplasty	Fresh frozen plasma
Outcome	Recovered following treatment	Normal in 1 week	Normal in 3 days			No detectable M band and remission of symptoms in 3 months	Recovered following surgery and treatment	Stable on subsequent follow-up

[Table/Fig-4]: Clinical histories and relevant findings of the patients.

Parameters	Case 1	Case 2	Case 3	Case 4	Case 5	Case 6	Case 7	Case 8	Biologic reference interval
PT (clot-based)	21.4	20.9	38.1	37.8	70.4	19	45	17.6	11-13.4 sec
PT Mixing Study	12.3	13.7	12.8	13.0	15.1	12.4	25.9	12.4	
APTT (clot based)	78.4	55.3	45.1	45.4	46.8	33.6	32.1	41.1	20.6-30.6 sec
APTT mixing study	28.1	26.2	27.8	24.2	26.7	22.8	24.5	26.9	
Thrombin Test (clot based)	16.5	16.5	18.8	19	17	22.9	16	21.3	16.4-18.8 sec
Fibrinogen (clot based)	320	274.5	432	345.2	394.6	176.4	432.2	104	250-520 mg/dL
Factor II (clot based)	82.4	78.3	15.5	15.7	24.6	87.7	117.4	31.2	70-120%
Factor V (clot based)	8.7	9.4	95.7	105.4	85.5	29.5	89.6	40	70-120%
Factor VII (clot based)	77.6	114.7	<5	21.4	<5	147.4	138.6	46	70-150%
Factor VIII (clot based)	3.6	22.2	116.7	98.3	127.3	137.6	125.7	158.1	70-150%
Factor IX (clot based)	89.3	94.9	34.3	8.5	7.9	93.9	104.7	24.4	70-120%
Factor X (clot based)	92.5	84	14.6	9.5	23.3	35.8	107.3	47.4	70-120%
Factor XI (clot based)	97.3	106.3	118.5	91.3	112.5	86.3	23.3	39.5	70-120%
Factor XII (clot based)	100.4	104.2	76.3	107.6	95.3	94.2	78.2	31.2	70-120%
vWF (immunoturbidometry)	145.9	116.4	137.6	144.7	126.4	106.9	16.4	186.9	47.8-173.2%

[Table/Fig-5]: Coagulation parameters of the patients.

DISCUSSION

The exact cause of MCFD can be either inherited or acquired [2]. They can range over a wide variety of aetiologies, which can include infections, inflammatory states, nutritional deficiencies, amyloidosis, sepsis, Disseminated Intravascular Coagulation (DIC), autoimmune diseases, liver diseases, or malignancies. While the prevalence of MCFD is comparatively low, the condition's rarity should not undermine its clinical importance [1,3].

The first two patients, cases 1 and 2, were found to have concomitant factor V and factor VIII deficiency (F5F8D). Soff and Levin classified Familial Multiple Factor Deficiencies (FMFD) into six types, and F5F8D is classified as FMFD I [4]. The first case of F5F8D was diagnosed in 1954 in a pair of Swiss siblings, and since then, less than 200 cases have been reported, with an estimated incidence of 1:1,000,000. Recently, there has been significant progress in understanding the underlying molecular mechanisms of these disorders [5-7]. For instance, F5F8D is primarily caused by mutations in two different genes (LMAN1 and MCFD2) that encode components of a stable protein complex. Overall, 33 LMAN1 and 17 MCFD2 pathogenic mutations have been detected so far [8]. This complex is linked and present in the secretory pathway of the cell and likely functions in transporting newly synthesised FV and FVIII, and perhaps other proteins, from the endoplasmic reticulum to the Golgi apparatus.

Clinically, they present with very mild symptoms and may be incidentally detected. As such, treatment options such as FFP are administered only if indicated, such as in both of the cases. Desmopressin acetate (DDVAP) may also be administered, though this raises only Factor VIII levels [9].

The next 3 cases (cases 3, 4, and 5) presented with bleeding disorders in the form of ecchymosis, and the coagulation panel revealed reduced levels of factors II, VII, IX, X, all of which are Vitamin K-dependent clotting factors. Despite the common laboratory picture, each case presented with a unique set of complaints and pathogenesis as highlighted in [Table/Fig-6].

Acquired causes of vitamin K deficiency should be evaluated and ruled out first due to their incidence. As seen in the present cases, they can have various causes including dietary insufficiency, drug intake, metabolic defects, liver diseases, malabsorption syndrome, sepsis, and altered gut bacteria. Inherited Vitamin K Clotting Factor

Variables	Case 3	Case 4	Case 5
Aetiology	Gallbladder disease and steatorrhea	Septicaemia	NSAIDs (over 2 years intermittently due to implant-associated pain) and alternate medications for 3 months to prevent COVID-19
Pathogenesis	Reduced absorption of vitamin K	Endotoxins interfere with vitamin K carboxylation of clotting factors. Sepsis without DIC	Altered gut microbiota, intestinal dysbacteriosis, drug interactions

[Table/Fig-6]: Aetiology and pathogenesis in the cases diagnosed with Vitamin K Dependant Clotting Factor Deficiency (VKDFD).

Deficiency (VKCFD) can be caused by mutations in the genes encoding γ-carboxylase or vitamin K epoxide reductase [10]. These two enzymes are key components of the carboxylation reactions which are vitamin K-dependant. Deficiency in either protein leads to under-carboxylation and hampers the activity of all the vitamin K-dependent coagulation factors, as well as several other proteins. In our case, the patient responded well to Vitamin K therapy, and due to the paucity of other systemic manifestations that are normally seen in inherited causes, acquired causes must first be considered and ruled out [11].

Multiple myeloma is known to interfere with the coagulation cascade, as the light chains bind with fibrinogen molecules, reducing functional activity. Additionally, they may bind with and interfere with both factors V and X. Multiple myeloma has a strong association with amyloidosis, which can also entrap factor X within the beta-pleated fibrils. However, factor X deficiency can occur in amyloid-negative multiple myeloma as well, as in case 6 [12].

Case 7 is a case of Heyde syndrome, a multisystem disorder characterised by the triad of gastrointestinal bleeding, acquired von Willebrand syndrome, and AS [13]. The high molecular weight multimers of von Willebrand factor are ineffectively cleaved due to obstruction to outflow, resulting in consumption and subsequent bleeding. In people with stenosis of the aortic valve, the valve becomes increasingly narrowed, which results in an increase in the speed of the blood through the valve to maintain cardiac output, in accordance with the Hagen-Poiseuille law. This combination of a narrow opening and a higher flow rate results in increased shear stress on the blood [14]. The von Willebrand normally uncoils into its active form at a site of damaged endothelium, further amplifying the haemostatic cascade. The higher shear stress seen in the narrowed valvular orifice in AS causes von Willebrand factor to uncoil as it would on encountering an injury site, albeit at a faster rate. Following this, it is degraded by its catabolic enzyme 'A disintegrin-like and metalloprotease domain with thrombospondin type 1 motifs' (ADAMTS13). This results in an unusable vWF, which is unable to bind to the collagen exposed at the site of injury [15]. As the amount of viable von Willebrand factor progressively decreases, the incidence of bleeding tendencies dramatically increases [8].

Liver disease results in various alterations in all three phases of haemostasis, as seen in case 8. This altered dynamic manifests as a fall in clotting factor levels, accompanied by a parallel fall in anticoagulant proteins. The liver plays a major role in blood coagulation, as it is the common site of synthesis of all clotting factors and their associated inhibitors, except for von Willebrand factor [8]. As a result, liver damage is commonly associated with impairment of coagulation. Overall, the haemostatic cascade must precisely balance between antithrombotic and prothrombotic processes to prevent excessive blood loss from injured sites on one extreme end and to prevent spontaneous thrombosis on the other. Liver failure causes multiple changes in the haemostatic system, as discussed earlier, because of reduced plasma levels of procoagulant and anticoagulant factors synthesised by the residual intact liver. Additionally, vitamin K deficiency may also co-exist in this state, resulting in defective or reduced gamma-carboxylation of vitamin K-dependent clotting factors and inhibitors.

Portal hypertension, with the development of collaterals and secondary splenomegaly, causes the sequestration of platelets within the spleen, resulting in thrombocytopenia. There may also be associated impairment in platelet function. Complications of cirrhosis, such as sepsis or variceal bleeding, may further accelerate the initiation of bleeding. Even though the liver is damaged, the ability of sinusoid endothelial cells to produce factor VIII remains intact. This may be due to increased production outside the liver, possibly as a response to the injury or as a side-effect of inflammation triggered by endotoxins. Additionally, the high levels of vWF can be explained by its non-hepatic origin, decreased breakdown by the liver, and reduced activity of ADAMTS13 [9]. These features suggest clotting factor deficiencies secondary to hepatic dysfunction. Elevated factor VIII levels were noted, which were explained by a compensatory production due to hepatocyte injury.

The prognosis and long-term management of MCFD depend on various factors, including the severity of the deficiency, the underlying cause, and the effectiveness of treatment. Contrary to single-factor deficiencies, which require a significant reduction in factor levels to produce bleeding symptoms, multiple factor deficiencies can produce a similar clinical picture even with mildly deranged values [6]. Regular monitoring of coagulation factor levels and the management of underlying conditions are crucial in preventing complications and improving outcomes.

CONCLUSION(S)

In the present case series, the treatment approach varied depending on whether the deficiency was inherited or acquired. For inherited MCFD, replacement therapy with specific deficient factors was the mainstay of treatment. However, for acquired MCFD, addressing the underlying condition or removing the triggering factor was found to be effective in normalising coagulation factor levels.

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