A Rare Cause of Isolated Prolonged Activated Partial Thromboplastin Time: An Overview of Prekallikrein Deficiency and the Contact System

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Abstract
Prekallikrein (PK) deficiency, also known as Fletcher factor deficiency, is a very rare disorder inherited as an autosomal recessive trait. It is usually identified incidentally in asymptomatic patients with a prolonged activated partial thromboplastin time (aPTT). In this article, we present the case of a 52-year-old woman, with no prior personal or family history of thrombotic or hemorrhagic disorders, who was noted to have substantial protracted aPTT through the routine coagulation assessment before a kidney biopsy. The patient had an uneventful biopsy course after receiving fresh frozen plasma (FFP). Laboratory investigations performed before the biopsy indicated normal activity for factors VIII, IX, XI, XII, and von Willebrand factor (vWF) as well as negative lupus anticoagulant (LA) screen. The plasma PK assay revealed low activity at 15% consistent with mild PK deficiency. The deficit of PK is characterized by a severely prolonged aPTT and normal prothrombin time (PT) in the absence of bleeding tendency. PK plays a role in the contact-activated coagulation pathway and the inflammatory response. Thus, other differential diagnoses of isolated prolonged aPTT include intrinsic pathway factor deficiencies and nonspecific inhibitors such as LA. We concluded that the initial evaluation of a prolonged aPTT with normal PT should appraise the measurement of contact activation factors and factor inhibitors. PK deficiency should be considered in asymptomatic patients with isolated aPTT prolongation, which corrects on incubation, with normal levels of the contact activation factors and factor inhibitors.

Keywords
prekallikrein deficiency, Fletcher factor deficiency, kallikrein-kinin system, activated partial thromboplastin time, prolonged aPTT

Introduction
The contact factor system (also called the kallikrein-kinin system) consists of 2 zymogens, factor XII and prekallikrein (PK), and 1 cofactor, high-molecular-weight kininogen (HMWK).1 These proteins are involved in blood coagulation, fibrinolysis, complement activation, renin-angiotensin hormonal regulations, and bradykinin formation. Initially, these proteins were thought to have a role in homeostasis due to the prolonged activated partial thromboplastin time (aPTT) related to factor XII, PK, and HMWK deficiency. This was proven incorrect due to the lack of a bleeding tendency seen in these factor deficient patients. However, studies suggest that a role in thrombosis independent of hemostasis is possible.2 In recent years, significant evidence has emerged implicating a role for these coagulation factors in tissue repair, inflammatory response, and innate immune system.3,4 In the normal state, the plasma kallikrein-kinin system contributes to basal bradykinin formation by PK activation for the maintenance of vascular homeostasis. When vessel injury occurs, activation of factor XII through contact activation participates in intravascular thrombus formation.1

Hereditary PK deficiency, also known as Fletcher factor (FF) deficiency, is a rare autosomal recessive defect usually diagnosed incidentally during routine coagulation tests demonstrating substantially prolonged aPTT and normal prothrombin time (PT) without associated bleeding diathesis.5,6 This condition is exceedingly rare; thus, the characterization of its phenotype is not well elucidated. In this article, we present the case of an asymptomatic 52-year-old Black
woman with a prolonged aPTT revealed during a routine workup before a scheduled procedure. A PK activator assay using patient plasma was consistent with PK deficiency.

**Case Presentation**

A 52-year-old Black woman was noted to have a prolonged aPTT before her elective kidney biopsy. The patient had been recently diagnosed with Sjögren’s syndrome and started on steroids. She then developed acute kidney injury associated with a positive antinuclear antibody (ANA) concerning for systemic lupus erythematosus (SLE) complicated by lupus nephritis. She had a history of bulimia with a recent weight gain of 11 kg during the past 2 months. Given abnormal coagulation laboratories, she was instead admitted for an expedited workup in the setting of rapidly progressive renal dysfunction with an elevation of creatinine from 1.1 to 1.8 mg/dL in the past 2 months. Given abnormal coagulation laboratories, she was instead admitted for an expedited workup in the setting of rapidly progressive renal dysfunction with a new disorder of coagulation. The patient had normal PT of 10.3 seconds (reference interval = 9.4-12.5 seconds), platelet count of 248,000/µL (reference interval = 200-450,000/µL), and fibrinogen level of 212 mg/dL (reference interval = 150-400 mg/dL). Thrombin time was slightly increased (18.7 seconds; reference interval = 15-25 seconds), and fibrinogen level was 212 mg/dL (reference interval = 150-400 mg/dL), with a repeat value of 83 seconds, as well as rapid progression of renal dysfunction with an elevation of creatinine from 1.1 to 1.8 mg/dL in the past 2 months. Given abnormal coagulation laboratories, she was instead admitted for an expedited workup in the setting of rapidly progressive renal dysfunction with a new disorder of coagulation. The patient had normal PT of 10.3 seconds (reference interval = 9.4-12.5 seconds), platelet count of 248,000/µL (reference interval = 200-450,000/µL), and fibrinogen level of 212 mg/dL (reference interval = 150-400 mg/dL). Other laboratory results were notable for stable normocytic anemia (hemoglobin 10.8 g/dL), without further hematologic abnormalities. A mixing study was ordered. The patient presented with high-grade proteinuria, anasarca, hypoalbuminemia, and urine sediment notable for fat droplets and lipid-laden casts, all consistent with acute nephrotic syndrome. Thus, a decision was made to pursue renal biopsy to further understand kidney disease and guide treatment.

Her current medication list included hydroxychloroquine, torsemide, prednisone, lisinopril, potassium chloride, and sumatriptan. The patient did not have any medical or family history of abnormal hemorrhagic or thromboembolic events. She had an uncomplicated Cesarean section in the past without any bleeding complications. She reported a prolonged aPTT of around 200 seconds in her sister, found incidentally through routine laboratory tests before shoulder surgery, without further hematologic follow-up. The patient’s physical examination did not show any evidence of ecchymoses, purpura, or petechiae.

The patient underwent the planned kidney biopsy after receiving 3 units of fresh frozen plasma (FFP) in light of the prolonged aPTT, which corrected the aPTT to 27 seconds. Kidney biopsy pathology showed class V membranous disease as well as evidence of proliferative disease with crescents. Possible causes of isolated prolongation of aPTT were considered, including heparin administration, inherited intrinsic pathway factor deficiencies, including XII, XI, IX, and VIII, factor inhibitors, and von Willebrand disease. The patient’s laboratory studies before biopsy indicated normal PT as well as a normal activity of factors VIII, IX, XI, XII, vWF, and HMWK. The lupus anticoagulant (LA) screen was positive, but the confirmatory test was negative. Anti-cardiolipin antibodies and β-2-glycoprotein 1 (immunoglobulins G and M) levels were normal. The plasma PK assay revealed low activity at 15% consistent with mild PK deficiency (reference interval = normal >50%, mild deficiency = 5% to 49%, severe deficiency ≤5%). The plasma PK was measured indirectly by quantifying the amidolytic activity of kallikrein by using a synthetic chromogenic substrate. Antigenic assays for evaluation of structure or quantity of PK were not available.

**Discussion**

PK deficiency is an uncommon coagulation disease considered not to be associated with bleeding tendency, despite marked aPTT prolongation. PK is the precursor of plasma kallikrein, a procoagulant and proinflammatory protease, that plays a role in the early stages of the intrinsic pathway of the coagulation cascade. It is synthesized primarily by the liver and mainly activated by factor XIIa or other substances such as endothelial cell prolylcarboxypeptidase (PRCP), which functions independently of factor XII.

The contact activation of the coagulation pathway is initiated by factor XII that is activated to XIa via binding to (“contact” with) negatively charged artificial or biological surfaces (contact activation). Factor XIIa proteolytically activates PK to form plasma kallikrein. Kallikrein, then, accelerates the activation of factor XI. This feedback loop amplifies factor XIa and PK production. Additionally, HMWK binds to PK and factor XI to facilitate their activation (Figure 1). Factor XIa also activates factor XI, leading to thrombin generation, fibrin formation, and platelet activation. Essentially, factor XIa initiates the intrinsic pathway of coagulation via its substrate, factor XI, and leads to the liberation of the proinflammatory mediator bradykinin by activation of the kallikrein-kinin system. The contact factor deficiencies do not result in a pronounced bleeding tendency as factor XI is additionally activated by platelets and thrombin.

Furthermore, PK is an important mediator of the inflammatory response. Thus, the kallikrein-kinin system can result in an inflammatory response via plasma kallikrein cleaving HMWK and releasing bradykinin. Bradykinin then binds to its constitutively expressed B1 (or B2) receptors. Activation of these receptors in return modulates endothelial cell proliferation, increases vascular permeability, resulting in vasodilation, edema, and hypotension (Figure 1). This system can be activated either by factor XIa formation or independently formed by PRCP.
It is known that PK deficiency is caused by mutations in the \textit{Klkb1} gene, located on chromosome 4q34-35, that are inherited via an autosomal recessive pattern. A homozygous point mutation (C529Y) has been identified as the genetic basis in severe cases. Hereditary PK deficiency was first described in 1965 by Hathaway et al who noted prolonged aPTT among the children of the Fletcher family. Initially, it was hypothesized that the prolonged aPTT was due to a missing new plasma thromboplastin factor, termed the “Fletcher factor.” The identity of the FF remained a mystery until 1973 when it was correctly recognized as PK, and the deficient plasma demonstrated abnormalities in the kinin, coagulation, and fibrinolytic systems. This discovery marked for the first time the interrelationship between these systems.

In PK deficiency, the activation process of factor XII occurs in a slow manner resulting in prolonged aPTT. The aPTT is a test for assessing the intrinsic and common pathways of the coagulation cascade from the contact phase system activation to fibrin formation. In this assay, the plasma is preincubated with an activator of the contact phase system (ie, silica, celite, kaolin, ellagic) to provide a negatively charged surface and a so-called partial thromboplastin (phospholipids, ie, cephalin). During the preincubation of plasma with the aPTT reagents (activated “surface” and partial thromboplastin), the contact phase of the blood coagulation is activated. Subsequently, the plasma is recalcified and the clotting time is measured. In the Fletcher trait, the aPTT autocorrects on prolonged incubation (after 1 hour) at room temperature (37 °C). This phenomenon is unique to PK deficiency and can be explained by the factor XII autoactivation instead of the faster kallikrein-mediated factor XIIa generation in a healthy person. Factor XIIa then activates factor XI, which leads to factor IXa determining the clotting time. PK cofactor is necessary for factor XIIa–mediated factor Xa, hence the failure to normalize aPTT in prolonged incubation time in PK deficiency patients.

Possible causes of elevated aPTT include deficiencies of factors VIII, IX, XI, vWF, PK, or HMWK and nonspecific inhibitors such as LA. The correction of the aPTT test after FFP administration supports the diagnosis of a factor deficiency in our patient and argues against the presence of a factor inhibitor.

In PK deficiency, the aPTT will correct to normal ranges with the addition of an equal volume of normal plasma after prolonged incubation. The rationale for administering FFP for abnormal coagulation stems from the fact that plasma is a depot of all coagulation factors. Plasma doses of 10 to 15 mL/kg typically result in an increase in coagulation factors by 15% to 20%, which reaches levels needed for normal hemostasis. Also, the effect of FFP replacement depends on the starting level of coagulation factors. For
**Table 1. Studies Reporting on Cases of Prekallikrein Deficiency.**

| Case | Year of publication | Author | Age (years)/sex | Degree of aPTT prolongation (reference values, seconds) | PK assay result and method | Outcome |
|------|---------------------|--------|-----------------|--------------------------------------------------------|---------------------------|---------|
| 1    | 2021                | This case | 52/Female | 106.4 (23-32) | PK:C 15% (normal = 50%, mild = 5 to 49% severe = <5%) | aPTT normalized after 3 units of FFP |
| 2    | 2020                | Barco et al | 68/Female | N/A | PK:C 1% | Surgery without complication |
| 3    | 2006                | Inoue et al | 47/Male | N/A | PK:C <1% | Surgery without complication |
| 4    | 2017                | Criel et al | 63/Male | 125 (24-36) | PK:C 1% | N/A |
| 5    | 2005                | Jones et al | 79/Male | 130 (24-36) | PK:C 4% | N/A |
| 6    | 2008                | Katsuda et al | 64/Female | 136.5 (40-100) | PK:C <1% | N/A |
| 7    | 2008                | Katsuda et al | 50/Female | 126.2 (40-100) | PK:C <1% | N/A |
| 8    | 2009                | Francois et al | 63/Male | 176 (<35) | PK:C <1% | N/A |
| 9    | 2010                | Francois et al | 32/Male | 140 (24-36) | PK:C 1% | N/A |
| 10   | 2011                | Francois et al | 38/Female | 109 (24-42) | PK:C <1% | N/A |
| 11   | 2012                | Francois et al | 38/Female | 222 (26-376) | PK:C 5% | N/A |
| 12   | 2013                | Francois et al | 38/Female | 169 (24-34) | PK:C 5% | N/A |
| 13   | 2014                | Francois et al | 32/Male | 140 (24-36) | PK:C <1% | N/A |
| 14   | 2015                | Francois et al | 55/Male | 222 (26-376) | PK:C 4% | N/A |
| 15   | 2016                | Francois et al | 15/Male | 169 (24-34) | PK:C 1% | N/A |
| 16   | 2017                | Francois et al | 43/Male | 109 (24-42) | PK:C 1% | N/A |
| 17   | 2018                | Francois et al | 38/Female | 105 (24-42) | PK:C 1% | N/A |
| 18   | 2019                | Francois et al | 48/Female | 117 (26-36) | PK:C <1% | N/A |
| 19   | 2020                | Francois et al | 66/Male | 112 (26-36) | PK:C <1% | N/A |
| 20   | 2021                | Francois et al | 36/Female | 62.2 (23-35) | PK:C <1% | N/A |
| 21   | 2022                | Francois et al | 50/Male | 140 (23-33) | PK:C <1% | N/A |
| 22   | 2022                | Francois et al | 32/Female | 99.4 (N/A) | PK:C 1% | N/A |
| 23   | 1982                | Raffoux et al | 11/Male | N/A | Fletcher factor level 0.41 U/mL (0.75-1.25 U/mL; ND) | Tonsillectomy performed with prolonged bleeding, which required transfusion of FFP and several sutures |
| 24   | 1980                | Waddell et al | 62/Male | 78 (N/A) | Fletcher factor clotting assay <1% | Tonsillectomy was performed with prolonged bleeding, which required transfusion of FFP and several sutures |
| 25   | 1980                | Waddell et al | 7/Male | 355 (N/A) | Fletcher factor clotting assay <0.01% | No abnormal bleeding in 2 years follow-up |

(continued)
| Case | Year of publication | Author | Age (years)/sex | Incidental finding of isolated prolonged aPTT prior to surgical or dental procedure | Degree of aPTT prolongation (reference values, seconds) | PK assay result and method | Outcome |
|------|--------------------|--------|----------------|--------------------------------------------------------------------------------|-----------------------------------------------|--------------------------|---------|
| 32   | 1990              | Castaman et al. | 38/Female | Yes | Race greater than 2 | PK:C <1%; PK:Ag negative (by electroimmunoassay) | No improvement in PK level after DDAVP |
| 33   | 1990              | De Stefano et al. | 49/Female | Yes | 116 (< 30.6) | PK:C <1%; PK:Ag 50% (by Laurell immunoelectrophoresis) | Total thyroidectomy without complication |
| 34   |                   |        | 51/Male | Case 34’s family member | 120 (< 30.6) | PK:C <1%; PK:Ag 34% (by Laurell immunoelectrophoresis) | PK:C <1%; PK:Ag 34% (by Laurell immunoelectrophoresis) | Total thyroidectomy without complication |
| 35   |                   |        | 47/Male | Case 34’s family member | 94 (< 30.6) |PK:C <1%; PK:Ag 34% (by Laurell immunoelectrophoresis) | PK:C <1%; PK:Ag 34% (by Laurell immunoelectrophoresis) | Total thyroidectomy without complication |
| 36   |                   |        | 38/Female | Case 34’s family member | 110 (< 30.6) | PK:C <1%; PK:Ag 34% (by Laurell immunoelectrophoresis) | PK:C <1%; PK:Ag 34% (by Laurell immunoelectrophoresis) | Total thyroidectomy without complication |
| 37   | 1970              | Hootsensky et al. | 77/Female | Yes | 135.9 (< 40.0) | Factor VIII clotting assay <1% | Closed reduction of the fracture without complication |
| 38   |                   |        | 6/Male | Case 34’s family member | 278.6 (< 40.5) | PK:C <1%; PK:Ag 34% (by Laurell immunoelectrophoresis) | PK:C <1%; PK:Ag 34% (by Laurell immunoelectrophoresis) | Total thyroidectomy without complication |
| 39   |                   |        | 50/Male | 170.0 (N/A) | PK:C <1%; PK:Ag 34% (by Laurell immunoelectrophoresis) | PK:C <1%; PK:Ag 34% (by Laurell immunoelectrophoresis) | Total thyroidectomy without complication |
| 40   | 2009              | Odumosu et al. | 25/Female | Yes | 69.4 (24-38) | PK:C <1% | Underwent hemorhoidectomy and polypectomy without complication |
| 41   | 2009              | van Veen et al. | 19/Male | Yes | 132 (23.5-37.5) | PK:C <1% | Underwent hemorhoidectomy and polypectomy without complication |
| 42   | 1995              | Dela Cadena et al. | 9/Female | Yes | 58 (< 38) | PK:C <1%; PK:Ag 20-25 (by ELISA) | Successful redo sternotomy and aortic valve replacement |
| 43   | 2008              | Dietzel et al. | 24/Male | Yes | N/A | PK:C <1%; PK:Ag normal (ND) | Dental extraction without complication |
| 44   | 1980              | Saade et al. | 29/Male | Yes | 67.7 (33-40) | Factor VIII clotting assay 1% | Renal surgery without complication |
| 45   | 1983              | Colla et al. | 20/Male | Yes | 131 (23-33) | Factor VIII clotting assay 1% | Renal surgery without complication |
| 46   | 1986              | Bouma et al. | 38/Female | Yes | N/A | PK:C <1%; PK:Ag 35% (ND) | Hysterectomy without complication |
| 47   |                   |        | N/A/Female | Case 47’s family member | N/A | PK:C <1%; PK:Ag 35% (ND) | Hysterectomy without complication |
| 48   |                   |        | N/A/Male | Case 47’s family member | N/A | PK:C <1%; PK:Ag 35% (ND) | Hysterectomy without complication |
| 51   | 2018              | Baker et al. | 15/Male | Yes | 50.2 (21-32) | PK:C <5% | FFP 15 mL/kg 1 hour before for normalization of PK and improved monitoring during surgery. Open cardiac surgical repair for ASD without complication |
| 52   | 1945              | Hatchway et al. | 11/Female | Yes | 250 (< 100) | First Factor VIII assay | Open cardiac surgical repair for ASD without complication |
| 53   |                   |        | 8/Female | Case 53’s family member | 208 (< 100) | PK:C <1% | Open cardiac surgical repair for ASD without complication |
| 54   |                   |        | 4/Female | Case 53’s family member | 174 (< 100) | PK:C <1% | Open cardiac surgical repair for ASD without complication |
| 55   |                   |        | 9/Male | Case 53’s family member | 168 (< 100) | PK:C <1% | Open cardiac surgical repair for ASD without complication |

Abbreviations: aPTT, activated partial thromboplastin time; PK, prekallikrein; PK:C, prekallikrein clotting assays; FFP, fresh frozen plasma; N/A, not available; PK:Ag, prekallikrein antigen; ELISA, enzyme-linked immunosorbent assay; ND, not described; TIA, transient ischemic attack; DDAVP, desmopressin; ASD, atrial septal defect.

*The decreasing/normalization of the aPTT with increasing preincubation time.
instance, if the levels are substantially low (very prolonged aPTT as presented in this patient), the plasma replacement may reflect significant improvement compared with those in whom the levels are mildly decreased. However, this is dependent on the specific sensitivity of the aPTT reagent to PK levels.

The patient also presented with a slightly increased thrombin time. Severe hypofibrinogenemia (<100 mg/dL) can extend the thrombin time. This can result from a complete lack of fibrinogen (afibrinogenemia), decreased amount of fibrinogen (hypofibrinogenemia), or the presence of dysfunctional fibrinogen (dysfibrinogenemia). Acquired conditions, such as liver or renal disease, amyloidosis, thrombolytic therapy, disseminated intravascular coagulation (DIC), malignancy, and thrombin inhibitors (heparin, dabigatran, argatroban, and hirudin), can also lead to reduced fibrinogen levels and hence prolonged thrombin time.18 Our patient did not present with any of these conditions, and she was not receiving any of these medications. Therefore, the normalization of the thrombin time indicates a likely artifact. It should be noted that despite a dysfibrinogenemia was not completely ruled out, it was unlikely given the normal fibrinogen and the normal postprocedure thrombin time.

Reports of PK deficiency diagnosed as an incidental finding of isolated prolonged aPTT before procedures have been published since 1965 (Table 1). These data have concluded that the prolongation of aPTT is due to PK deficiency: the characteristic normalization of the severely prolonged aPTT following increased preincubation time is due to autoactivation of factor XII.19 However, this is dependent on the specific sensitivity of the aPTT reagent to PK levels.

The case of PK deficiency described in this report was uncovered after the incidental finding of prolonged aPTT that could suggest a mode of inheritance. We concluded that the initial evaluation of a patient with a prolonged aPTT should raise the possibility of PK deficiency especially if the aPTT corrects on extended incubation.

**Author Contributions**

Ivy Riano and Klaorat Prasongdee wrote the original draft of the paper. All authors read and approved the final manuscript. All authors had access to the data and a role in writing this manuscript.

**Declaration of Conflicting Interests**

The author(s) declared no potential conflicts of interest with respect to the research, authorship, and/or publication of this article.

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**Ethics Approval**

Our institution does not require ethical approval for reporting individual cases or case series.

**Informed Consent**

Verbal informed consent was obtained from the patient for her anonymized information to be published in this article.

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