Prekallikrein (Fletcher Factor) Deficiency*

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ABSTRACT

One new case and 29 reported cases of hereditary prekallikrein (Fletcher factor) deficiency are reviewed. Abnormalities in the coagulation, fibrinolytic, complement, and kinin systems are described. These cases are discovered incidentally by prolonged partial thromboplastin times (PTTs) which correct with extended incubation in the presence of a contact activator. Prekallikrein levels are less than two percent of normal levels. In general, the remainder of the coagulation profile is normal, and no bleeding diathesis is present. Most patients are black and the incidence of consanguinity is increased. The disease is transmitted in an autosomal recessive manner. Acquired Fletcher factor disease is a moderate prekallikrein deficiency present in many common disease states. Its clinical significance is largely unknown. Both acquired and hereditary forms may rarely predispose to thrombotic phenomena.

Introduction

The interrelationships between the coagulation, fibrinolytic, and kinin systems were virtually unknown in the 1960s. The first clue to elucidating these interrelationships came in a case report of a new coagulopathy. A cabin fire in the mountains of eastern Kentucky in 1963 caused several members of the Fletcher family to be hospitalized for burns and frostbite. When 11-year-old B. Fletcher was evaluated for possible adenoidectomy, her partial thromboplastin time (PTT) was elevated. An extensive workup at the University of Kentucky Medical Center revealed that four of the Fletcher siblings had prolonged PTTs that corrected with incubation in the presence of glass. Nearly every other coagulation parameter was normal and there was no history of abnormal bleeding. It was hypothesized that the prolonged PTT was due to a missing new plasma thromboplastin factor, termed the Fletcher factor. Hence, the coagulopathy was called Fletcher factor deficiency. The identity of the Fletcher factor remained a mystery until 1973 when it was correctly identified as prekallikrein, and the deficient plasma demonstrated abnormalities in the kinin, coagulation, and fibrinolytic systems. This discovery was received with astonishment because it marked the first time that these systems had been linked.

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Later defects in chemotaxis were also observed.\textsuperscript{26} These important discoveries led to more case reports of Fletcher factor deficiency and further experimentation into the intricacies of contact activation.

In the 1970s, researchers discovered that prekallikrein levels were well below normal values in many common though often life threatening disease states.\textsuperscript{19} In contrast to the severe deficiency seen in the hereditary form, acquired prekallikrein deficiency had only moderately depressed prekallikrein levels.\textsuperscript{19} Its clinical significance is largely unknown.

A case of prekallikrein deficiency is described and a literature review is presented.

**Case Report**

A 42-year-old black male was admitted for an elective hemorrhoidectomy in January, 1980. He developed hemorrhoids in adolescence and was plagued since then with episodes of rectal pain and pruritis. He observed blood on his toilet paper but no gross blood in his stools. He had two prior tooth extractions which bled for two to three days each before hemostasis was obtained. However, a tonsilectomy, subsequent tooth extractions, a benign suprACLavicular node excision, and removal of an osteoma from the roof of the mouth were all completed without abnormal bleeding. He denied a history of epistaxis, bruising, and joint pain. Family history was negative for bleeding problems. The physical examination was within normal limits except for hemorrhoids. A preoperative PTT was 89 seconds but corrected to 29 seconds after incubation for 30 minutes in the presence of micronized silica. The hematocrit, hemoglobin, white blood count, prothrombin time, bleeding time, platelet count, fibrinogen and Factor XI and XII assays were all normal. The patient underwent proctosigmoidoscopy and hemorrhoidectomy without complications.

**Literature Search**

A medline computer search was performed at the Jesse Jones Library in Houston, TX on the subject of prekallikrein (Fletcher factor) deficiency and the references were screened for case histories. Each case was reviewed for age at diagnosis, sex, prekallikrein level, bleeding diathesis, PTT, surface activator used in the PTT test, incubation time of plasma with the activator, prothrombin time (PT), thrombin time (TT), hemoglobin, hematocrit, platelet count, bleeding time, factors VIII, IX, XI, and XII, family history of bleeding, parent's race and prekallikrein level. Bleeding times, PTTs, PTs, and TTs were determined using conventional methods and the references should be consulted for specific details. For the methodology of fibrin plate assays, clot lysis times, amidolysis tests, permeability enhancing system tests, and bradykinin determinations the references in which each result was mentioned should be consulted.

**Review of Literature**

Most of the data compiled from cases of hereditary prekallikrein factor deficiency are listed in table I. A few abnormal findings are summarized in the following text. In addition, laboratory tests concerning fibrinolytic, chemotactic, and kinin systems are presented. Finally, data on acquired prekallikrein deficiency are given.

Thirty cases of hereditary prekallikrein deficiency were reviewed. The average age at diagnosis was 30 years with a range of five months to 83 years. Of 27 cases reporting sex, 20 were males and seven were females.

Hemorrhagic tendencies were described in five of the 29 cases. One patient presented with recurrent hemarthroses and hematomas with no history of prior trauma.\textsuperscript{10} One case presented with recurrent epistaxis and required transfusion of fresh frozen plasma and several sutures after suffering prolonged bleeding during a tonsillectomy.\textsuperscript{18} One patient presented with frequent epistaxis,\textsuperscript{17} one had hemorrhagic cystitis,\textsuperscript{25} and another had rectal bleeding,\textsuperscript{13} however, none of the investigators attributed
Clinical and Laboratory Data on Patients with Prekallikrein Deficiency

**Prekallikrein (Fletcher Factor) Deficiency**

**Table I**

<table>
<thead>
<tr>
<th>Cases</th>
<th>Age (Years)</th>
<th>Sex</th>
<th>Prekallikrein Level</th>
<th>Surface Contact</th>
<th>PTT Incubation (Sec)</th>
<th>Time Incubation (Min)</th>
<th>Factor XII</th>
<th>Parent's guinity</th>
<th>Reference</th>
</tr>
</thead>
<tbody>
<tr>
<td>BF</td>
<td>11</td>
<td>F</td>
<td>-</td>
<td>Glass</td>
<td>250</td>
<td>-</td>
<td>-</td>
<td>ABN</td>
<td>White*</td>
</tr>
<tr>
<td>LF</td>
<td>8</td>
<td>F</td>
<td>-</td>
<td>Glass</td>
<td>203</td>
<td>240</td>
<td>35</td>
<td>NL</td>
<td>1</td>
</tr>
<tr>
<td>CF</td>
<td>4</td>
<td>M</td>
<td>-</td>
<td>Glass</td>
<td>174</td>
<td>240</td>
<td>43</td>
<td>NL</td>
<td>1</td>
</tr>
<tr>
<td>WF</td>
<td>9/12</td>
<td>M</td>
<td>-</td>
<td>Glass</td>
<td>168</td>
<td>-</td>
<td>-</td>
<td>NL</td>
<td>1</td>
</tr>
</tbody>
</table>

1. 77 F 1% Kaolin 135.9 10 36.6 NL White

2. 6 F 1% Kaolin 184.7 10 62.6 ABN Black

3. 50 M 1% Kaolin 170.0 10 48.1 ABN Black

1. 44 M 1% Glass 89.3 10 46.4 NL White

1. 7/12 M - Kaolin 124 10 54 NL Black

MC 12 F <1% Kaolin 135 10 40 NL White Yes

AC 16 F <1% Kaolin 143 10 38 NL

ESC 18 F <1% Kaolin 111 10 39 NL

1. 29 M 1% Particulate Activator 78 15 35 NL Black

1. 62 M 1% Particulate Activator 78 15 35 NL Black

1. 60 M - Prolonged 5 Normal NL

1. 35 M <1% - Prolonged - Normal - Black

2. 75 M <1% - Prolonged - Normal - Black

3. -- -- <1% - Prolonged - Normal -

1. 83 M 1.7% Particulate Activator >95 20 49.2 NL Black

1-8 6 M-6 Unk <1% - Prolonged - Normal - Black-6

1. 7 M <1% - 355 10 33.8 ABN Black No

1. 11 M <1% - Prolonged - Normal - White No

1. 42 M - Silica 89 30 29 NL Black

- Data not available.
- UNK = unknown.
- NL = > 40 percent.
- ABN = < 40 percent.
- Father was "Part Black".
+ Cases represented with initials are sibling. Numbered cases are unrelated.

Bleeding in these cases to prekallikrein deficiency.

Prekallikrein levels were less than two percent of normal in 23 of 23 cases that reported this data. However, in 18 cases of prekallikrein deficiency, only five patients had antigenic material similar to prekallikrein (cross reacting material or CRM). This indicates that in these five cases, CRM was nonfunctional. The hematocrit and hemoglobin values were published in 11 of the 30 cases and eight of these were normal. Of the remaining three, one patient had a microcytic anemia, one had a hematocrit of 29 percent apparently due to bleeding, and one
had a hematocrit of 16 percent owing to chronic lymphocytic leukemia. The bleeding time was normal in 13 of 13 reported cases. The platelet count was normal in 13 of 14 reported cases and appeared increased in one case.

The PTT was prolonged in all cases and was greater than 67 seconds in 17 of 17 cases reporting a specific value. The PTT returned to the normal range after 10 to 30 minutes of incubation time in 12 of 15 cases reporting this data. Of the remaining three cases, two required an incubation time of 240 minutes and one of five minutes. Commonly used activators which were reported in 15 cases included glass, kaolin, and silica. Ellagic acid was insensitive in detecting one patient with Fletcher factor deficiency.

The prothrombin time and thrombin time were normal in all cases reporting this data. Assays for factors VIII, IX, and XI were all normal. Factor XII assays were normal in 14 of 18 cases. One case was described with a partial Hageman factor deficiency, while abnormal factor XII assays were reported in two of Hattersley’s patients and one of Hathaway’s.

Family studies revealed no history of excessive bleeding in nine of 10 families. There was one report of a maternal aunt suffering frequent epistaxis. Only four articles commented on consanguinity, and two of four families interviewed involved consanguinity. Of 21 sets of parents, the father was black in 16, “part black” in one and white in four. Of the mothers, 16 were black and five were white. The father’s prekallikrein levels were reported as “heterozygote” levels in four of four cases. The mother’s prekallikrein levels were reported as “heterozygote” in three cases, normal in one case, and 170 percent normal levels in another case. None of the parents tested had a prolonged PTT. Three papers hypothesized that the genetics of hereditary Fletcher factor deficiency is autosomal recessive with a prolonged PTT only in the homozygotes. One author proposed an autosomal dominant transmission. Prekallikrein levels in eight offspring of a Fletcher factor deficient patient revealed a mean prekallikrein level of 53 percent with a range of 40 to 72 percent.

Abnormalities in the kinin and fibrinolytic systems have also been described. Prekallikrein deficient plasma failed to yield kinins as opposed to normal controls. Prekallikrein factor deficient patients also had abnormal chemotaxis and abnormal permeability enhancing systems. Ellagic acid mixed with normal and prekallikrein deficient plasma revealed that vascular permeability generated from normal plasma was much greater than the prekallikrein deficient plasma. Clot lysis time of a prekallikrein deficient plasma was 78 minutes compared to 11 minutes after the addition of prekallikrein to the plasma. Abnormally high clot lysis time and abnormal fibrin plate and amidolytic assays for prekallikrein were also reported in subsequent studies. There has been only one case of myocardial infarction in a hereditary prekallikrein deficiency patient.

Acquired Fletcher factor deficiency has been defined as prekallikrein levels more than two standard deviations below the mean for normal subjects. Ragni et al studied 315 consecutive patients undergoing coagulation profiles and found that 67 had acquired prekallikrein deficiency. Partial prothrombin time was prolonged in 41 (61 percent) cases. Prekallikrein levels ranged from 23 to 35 percent of normal. Acquired prekallikrein deficiency has been reported in liver disease, septic shock, chronic renal failure, vitamin K deficiency, multiple trauma, disseminated intravascular coagulation, typhoid fever, blood component therapy, deep vein thrombosis, and phle-
Prekallikrein was one of many plasma proteins decreased in these disease states. Deficiencies of high molecular weight kininogen, factor XII, antithrombin III, and fibrinogen have all been associated with prekallikrein deficiency in septic shock. Two cases of thrombophlebitis in acquired prekallikrein deficiency have been reported.

**Relationship of Prekallikrein with other Proteolytic Systems**

Fletcher factor is intimately involved with coagulation, fibrinolytic, kinin and complement systems. The relationship is shown in figure 1.

Participants in the contact phase of coagulation include Hageman factor (factor XII), prekallikrein, high molecular weight kininogen (HMWK) and factor XI. Factor XII is activated to XIIa on a negatively charged surface. Factor XIIa activates prekallikrein to kallikrein. Only a small concentration of XIIa is sufficient to activate prekallikrein. Kallikrein, then, speeds up the activation of factor XII remaining in the system. The HMWK binds prekallikrein and factor XI to the surface thus facilitating their activation. Thus, in prekallikrein deficiency, the activation of factor XII and, therefore, the intrinsic pathway of coagulation, proceeds slowly resulting in prolongation of PTT. Increasing the contact time of plasma with activator in the PTT test from normal three to five minutes to 10 minutes or more can generate enough XIIa through surface contact to normalize the PTT in patients with prekallikrein deficiency.

The fibrinolytic system is responsible for clot lysis. The active enzyme which brings about dissolution of clot is plasmin which is an activated form of plasminogen. Plasminogen is activated by several activators which include Factor XIa, Xa, streptokinase and urokinase. Recently it has been shown that kallikrein is also a potent activator of plasminogen. Thus the fibrinolytic system is closely knitted with the prekallikrein. It is, however, not yet clear whether or not prekallikrein plays a major role in the fibrinolytic pathway, although individuals with prekallikrein deficiency may have a predisposition to thromboembolism.

![Figure 1](image-url)
Prekallikrein appears to be involved in the kinin system as well. In human plasma, multiple types of kininogens exist. Two major classes are high molecular weight kininogens (HMWK) and low molecular weight kininogens (LMWK). Kallikrein has the property of splitting off active polypeptides from HMWK. These fragments, known as kinins, enhance vascular permeability, dilate certain blood vessels, contract certain smooth muscles, and perhaps bring about migration of leukocytes in extravascular space.\(^\text{16}\)

The complement system is a complex system involved in the mediation of inflammation and tissue damage. Factor XIIa through generation of plasmin can initiate the classical pathway of complement activation.\(^\text{16}\) Similarly the breakdown products of HMWK have complement augmentation effect.\(^\text{16}\) Thus, prekallikrein may affect the complement system indirectly through activation of XII and breakdown of HMWK. The clinical significance of this apparently minor influence is not known.

In the large majority of cases, prekallikrein deficiency is a laboratory nuisance, especially in the preoperative screening of patients for surgery. A prolonged PTT triggers a hemostatic alarm and necessitates the performance of several complex and time consuming tests to elucidate the problem. This causes delays in the surgery schedule. Awareness of the problem and screening for prekallikrein deficiency could spare time and unnecessary expense to the patient.

References


