Review Article

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Journal of Molecular Genetics and Medicine

2018
Vol.2 No.1:1

Critical Analysis of the Patients with Congenital Prekallikrein Deficiency and a "Purported" Bleeding Tendency

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Received date: November 24, 2017; **Accepted date:** December 24, 2017; **Published date:** January 2, 2018

Citation: Girolami A, Cosi E, Ferrari S, Santarossa C (2018) Critical Analysis of the Patients with Congenital Prekallikrein Deficiency and a "Purported" Bleeding Tendency. J Mol Genet Med Vol.2 No.1:1

Abstract

Objective: To analyse the bleeding manifestations presented by some patients with congenital prekallikrein deficiency.

Patients and methods: 106 papers dealing with patients with prekallikrein deficiency were obtained by a time unlimited PubMed Search and by the revaluation of personal files dealing with patients with prekallikrein deficiency. Only proven or highly probable cases of congenital deficiency were included. Acquired defects were excluded.

Results: Out of the 106 papers examined, eleven patients were reported to manifest a variable bleeding tendency. Bleeding was usually mild (epistaxis, easy bruising, bleeding after oral or nasal surgery). It was severe in one infant (hematomas, hemarthrosis). Transfusion therapy with whole blood or fresh frozen plasma was used in 4 patients. In only two instances there are the demonstrations of a reduction or stoppage of bleeding after administration of Fresh Frozen Plasma. The rest of these purported bleeders underwent tonsillectomy, delivery and other surgical procedures without undue bleeding. Local factors or transient coagulation defects are the likely explanation for the occasional bleeding manifestations observed. The mutations found in the three patients who were investigated by molecular biology techniques were Gly401Glu (two cases) and Cys529Tyr (one case).

Conclusion: An analysis of the cases of Prekallikrein deficiency and bleeding suggests that these patients need no replacement therapy but in the case of surgery requiring cardio-pulmonary bypass procedures and heparin administration. In this case the basic prolongation of the clotting tests may complicate the evaluation of the effect of heparin.

Keywords: Prekallikrein; Bleeding; Surgery; Contact phase; Coagulation

Introduction

Prekallikrein (PK) is a protein involved in the contact phase of blood coagulation. It circulates both as free (25%) and as complexed with high molecular weight kininogen (HMWK) (75%). Once activated by aFXII, PK is transformed into Kallikrein. Kallikrein has two main functions, namely 1) it causes vasodilation and hypotension by liberating bradikinin from HMWK and 2) it stimulates fibrinolysis by stimulating plasminogen activation [1]. PK deficiency is a rare condition. Only about 150 cases have been reported [2]. However, it is likely that many cases go undetected since the patients are asymptomatic. Most cases are discovered during the routine evaluation carried out before a surgical procedure.

It is widely accepted that patients deficient in PK show no bleeding similarly to those with FXII deficiency [2].

However, an analysis of all reported case of PK deficiency reveals that in a few instance a variable bleeding diathesis is occasionally reported [3-15].

The purpose of the present study is to analyse critically the purported bleeding tendency of these patients. The clarification of this problem is in line with the recent revival of interest in the disorders of the contact phase of blood coagulation [16-19].

Patients and Methods

All patients with congenital PK deficiency and a purported bleeding tendency were gathered from two sources, namely: 1) personal files pertaining to previously studied patients with this coagulation disorder and 2) from two, time unlimited, Pub Med searches carried out in Jan 2010 and in Jan 2017 using appropriate key words including the Mesh items suggested by Pub Med. Side tables were also consulted when available. All pertinent papers were obtained with the help of the Padua University Pinali Medical Library. Cross checking of the references listed at the end of each paper was carried out by two of us in order to avoid omissions. Out of a total of 106 papers examined, we found eleven articles which dealt with 11 patients for whom the existence of a bleeding tendency was reported. The inclusion criteria were a sure or a highly probable diagnosis of PK deficiency based on the following

findings: 1) a prolonged PTT corrected by the addition of normal plasma or serum; 2) a normal PT; 3) PK activity level of less than 15% of normal; 4) shortening of the aPTT on prolonged incubation times; 5) Normal FXII and FXI. PK antigen levels and molecular analysis of the defect were not considered as inclusion criteria since they were available only for a minority of patients. However, these data were always recorded whenever available. Cases without adequate clinical data were excluded. Acquired cases with PK deficiency were also excluded.

Results

The number of papers dealing with congenital PK deficiency that claimed the existence of a variable bleeding tendency was eleven. The main features of these patients are gathered in **Table 1**. Seven were male and four females. Age varied between 4 and 75 (mean age 37.5 years). PK activity varied between 1 and 13% of normal. PK antigen was evaluated only in three patients and was very low (1% of normal) in two cases and 25% of normal in the other patient. 11 patients, out of a pool of about 100 cases, represent 10% of cases. In all the remaining 90 cases of PK deficiency no excessive bleeding was ever noted. In only three of these patients, molecular biology techniques were used to confirm the diagnosis. The mutations involved were Gly401Glu (two cases) and Cys529Tyr (one case). In the remaining patients, diagnosis was made or purported on clotting tests and assays.

Bleeding manifestations were in general mild, epistaxes, easy bruising, bleeding after tonsillectomy. Only in one instance hemarthrosis was reported. Due to the mildness of bleeding, little information are available about replacement therapy which was reported only in a few cases. In one instance, a patient with chronic lymphocytic leukemia and hematuria, it was given as a supportive measure [14]. In another case a unit of whole blood was given after tonsillectomy [4]. In only two instances there was the demonstration that the administration of Fresh Frozen Plasma (FFP) stopped or decreased the bleeding which occurred in one patient after ethmoidectomy and nasal polypectomy after the removal of nasal tampons [12] and in another patient, after tonsillectomy [9].

Table 1 Main features of patients with prekallikrein deficiency and "purported" bleeding manifestations; NR: Not Reported; CLL: Chronic Lymphocytic Leukemia.

Authors (year)	Age (years), gender	PK activity	PK antigen	Type of bleeding	Associated condition	Transfusion	Genotype	Mutation (exon)	Comments
Hathaway et al. (1965) [3]	77, F	1	NR	Easy bruising	None	None	Hom	NR	Hysterectomy and several tooth extractions without bleeding
Essien and Ebhota (1977) [5]	4, M	NR	NR	Hematomas, hemarthrosis	None	None	?	NR	No bleeding after circumcision
Aznar et al. (1978) [4]	12, F	NR	NR	Bleeding after tonsillectomy	Arthrogryposis	One unit of whole blood after tonsillectomy	Hom	NR	Two sisters similarly affected but asymptomatic
Waddell et al. (1980) [14]	62, M	1	1	Hematuria	CLL with bladder infiltration; mild thrombocytopenia	FFP as supportive measure	Hom	NR	Fatal due to hematuria and sepsis
Poon et al. (1982) [7]	7, M	1	1	Epistaxis	None	None	Hom	NR	
Raffoux et al. (1982) [9]	11, M	1.2	NR	Recurrent epistaxis, bleeding after tonsillectomy	None	FFP after tonsillectomy	Hom	NR	Sutures also needed after tonsillectomy
Sollo et al. (1985) [13]	49, M	NR	NR	Bleeding after two tooth extractions, hemorrhoids	None	None	Hom	NR	No bleeding after tonsillectomy and after tooth extractions
Castaman et al. (1990) [6]	22, F	1	Traces	Epistaxis in childhood	None	None	Hom	NR	Tonsillectomy and appendicectomy without bleeding

Shygekiyo et al. (1993-2003) [11,12]	44, M	1	25	Epistaxis post ethmoidectomy, post nasal tampons removal	Chronic sinusitis; nasal polyp	FFP after ethmoidectomy and nasal tampons removal	Hom	Gly401Glu (18)	One sister similarly affected but asymptomatic
Dasanu and Alexandrescu (2009) [8]	75, F	13	NR	Epistaxis	Hypertension	None	Hom	Cys529Tyr (14)	Patient had seven deliveries without bleeding
Nagaya et al. (2009) [15]	69, F	1	NR	Purpura, superficial hematomas	None	None	Hom	Gly401Glu (11)	

Discussion

An analysis of the bleeding manifestations presented by these patients will clarify their significance and their relation to the PK deficiency. One should start from the purported more severe case [5]. Unfortunately, the diagnosis of PK deficiency in this patient (an infant) studied in Africa is doubtful since there is no specific PK assay or an adequate substrate. Furthermore, there is no family and genetic study. Finally, the patient is reported to have hematomas and hemarthrosis which have never been reported in other patients with PK deficiency. Since there is no specific assay for FXI, it is likely that the patient had either FXI deficiency or a combination of PK and FXI deficiency. The clinical picture improved with time, and therefore it is also likely that the patient might have had an acquired condition (post-infection anticoagulants?) which subsequently disappeared. At the age of 4, the patient underwent circumcision in a hospital setting with non-excessive bleeding [5]. Such a surgical procedure is widely known as a cause of bleeding in patient with a hemorrhagic diathesis.

The other widely cited patient is that presented by Dasanu et al. [8]. This is a 75 year old hypertensive lady who presented mainly epistaxis. The diagnosis seems established since a mutation was found (Cys529Tyr) even though there was no family study. The most likely explanation is that the epistaxes were secondary to the hypertension. This is confirmed by the observation that the patient had seven vaginal deliveries and no bleeding ever occurred [8]. In this regard it is important to note that the same mutation (Cys529Tyr) of exon 14 was reported in other patients with PK deficiency that showed no bleeding tendency [20]. Several other patients manifested epistaxes. However, epistaxis is a common event and therefore, it cannot be maintained, by itself, to indicate a bleeding tendency. Epistaxis occurs often in young boys who are known to be prone to traumas. The same has probably occurred for some patients with PK deficiency.

It is likely that, under the impression of the prolonged aPTT, casual and minor bleeding manifestations that occur even in normal subjects were associated to the clotting defect. The association with an unknown defect is unlikely even though not completely excluded. Occasional bleeding occurring even in normal subjects probably are at the basis of the patients presented by Castaman et al. [6], Poon et al. [7] and others [13,14].

This is well confirmed by the fact that these patients underwent several surgical procedures, tooth extraction and tonsillectomy, without undue bleeding. It has an historic value in this regard the observation that the index patient with this disorder was described to have easy bruising. However, the same patient had undergone hysterectomy and several tooth extractions without any undue bleeding [3].

The only cases that present some nosological problems are the patients reported by Aznar et al. [4] and by Raffoux et al. [9]. These patients (children) presented in fact several bleeding manifestations (recurrent epistaxis and bleeding after tonsillectomy that required administration of whole blood or fresh frozen plasma FFP and sutures). Unfortunately, we do not know the mutation present in these patients. The most likely explanation is the association with an unknown or unrecognized defect (for example von Willebrand disease) or a specific mutation in the PK gene that may cause bleeding. This is remote but cannot be completely excluded on the basis of recent studies on the Arg596 mutations in FII or the Arg338Lys mutation in FIX [21,22]. Another patient (an adult) presented by Shigekiyo et al. [11] deserves also attention because he presented recurrent epistaxis and important bleeding after ethmoidectomy and nasal polyp removal. In this case it was also demonstrated that the administration of FFP stopped the bleeding that occurred after the removal of the nasal tampons [12]. However, it has to be remembered that the patient had chronic sinusitis which is often associated with local blood congestion and even spontaneous minor oozing of blood.

In conclusion, it seems safe to assume that PK deficiency is not accompanied by a bleeding tendency [2]. The few cases purported to have presented one may be probably explained on the basis of the following considerations: 1) suggestion by the prolonged aPTT; 2) automatic attribution of common bleeding manifestations to the clotting defect; 3) wrong or incomplete diagnosis; 4) co-existence of an unrecognized defect; 5) exaggeration of common bleeding manifestations because of the clotting defect. A combination of events may also be present.

It has to be remembered that a bleeding diathesis has to be characterized by multiple bleeding manifestations, occurring repeatedly in different sites and settings. None of the above mentioned patients met these criteria. Bleeding was always limited to the nasal or buccal mucosal, safe for the infant who was reported to have hematomas and hemarthrosis but then at the age of 5 underwent circumcision without bleeding.

Contrary to what seen for bleeding, PK deficiency has been maintained to have a plausible link with arterial and venous thrombosis [23-26].

It is important that physicians know that PK deficiency needs no specific prophylaxis or therapeutic measures, even during surgical procedures. The only exception to this rule may occur during cardiopulmonary by-pass procedures that require heparin administration [27-29]. In this case, due to the basal great prolongation of the aPTT, the administration of heparin could yield extremely prolonged assays that could be difficult to interpret. In this case the concomitant or prior administration of FFP could make the follow-up of heparinization much easier. This is the only time that patients with PK deficiency need a correction of the clotting defect [27-29]. The lack of bleeding in PK deficiency is in agreement with what observed in FXII and high molecular weight kininogen deficiencies. The only defect involved in the contact phase of blood coagulation accompanied by a haemorrhagic diathesis is that of FXI deficiency.

Acknowledgement

This study was supported in part by the "Associazione Emofilia ed altre coagulopatie delle Tre Venezie".

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