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Research Article

Similarities and Discrepancies in Patients with Congenital Factor FXII or Pre kallikrein Deficiency

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2. Keywords

Factor XII; Prekallikrein; Thrombosis; Hypertension; Bleeding

1. Abstract

1.1. Objectives: FXII and PK are two major components of the contact phase of blood coagulation.

The two factors are similar and their deficiency is not accompanied by bleeding. It is still unknown if some differences are present with regard to thrombosis.

1.2. Material and methods: all patients with these disorders studied in Padua during the past 50 years together with reported cases of the literature have been evaluated. Patients from the literature have been obtained by several, time unlimited, PubMed searches carried out in the years 2003-2018.

Only patients with a factor level of less than 15% of normal were included.

1.3. **Results:** the combined sources of our files and the PubMed searches yielded 246 cases of FXII deficiency and 106 patients with Prekallikrein deficiency.

No patient with bleeding was noted in FXII deficiency whereas two cases of Prekallikrein deficiency were reported to have a post surgical bleeding which stopped after replacement therapy. 37 cases of arterial or venous thrombosis were noted among patients with FXII deficiency whereas 20 were present in those with Prekallikrein deficiency. Hypertension was rare in FXII deficiency whereas it was frequent in Prekallikrein deficiency.

1.4. Conclusions: neither FXII deficiency or Prekallikrein deficiency are able to protect from thrombotic events. Due to the fact that the patients, being asymptomatic, are usually reported only or mainly when associated with another co-morbidity, it is clear that the figures here reported are only indicative and are significant only in stating that thrombosis, both arterial and venous may occur in these patients.

3. Similarities and Discrepancies in Patients with Congenital Factor FXII or Prekallikrein Deficiency

FXII and PK defect have a lot in common. They are both glycoproteins of a similar molecular weight; the first activates the second which, by its turn, once activated, potentiates the activation of the first protein [1]. Both these defects do not show a bleeding tendency, even though the title of the paper that reported the index patient with FXII deficiency read "A Familial hemorrhagic trait associated with a deficiency of a clot a promoting fraction of plasma [2]. As far as thrombotic events are concerning, matters seem a little more complicated.

At the beginning, about 40 years ago, it was commonly thought that FXII deficiency was associated with an increased incidence of thrombosis. This was mainly based on the great impact caused among the scientific community, by the death of the index patient with FXII deficiencies, namely Mr. Hageman, due to Pulmonary embolism [3].

This event had been overemphasized without realizing that the thromboembolism presented by Mr. Hageman had occurred after an accident that had caused hip fractures and bed immobilization [3].

Other studies, subsequently, have shown that the defect is not associated with an increased incidence of thrombosis [4,5].

Contrary to FXII deficiency, which has never been associated

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with excessive bleeding, PK deficiency was occasionally reported to be so [6].

The majority of these cases have been demonstrated to be untenable because of historical or laboratory inadequacies [6]. However, in at least two cases the bleeding remained unexplained and was corrected by replacement therapy [7-9].

Despite these few exceptions, it is commonly accepted today that even PK deficiency is not accompanied by bleeding [6]. Thrombotic events, both arterial and venous have been often reported in PK deficiency [10] (**Table 1**).

The purpose of the present study is to investigate the presence of similarities or discrepancies in the number of thrombotic events seen in these two diseases.

Table 1. Similarity and differences between FXII and Prekallikrein.

Features	FXII	PK	Comments
Structure	Glycoprotein	Glycoprotein	
molecular weight	80.000 Dalton	88.000 Dalton mostly combined with HMWK	Only about 25% of PK is free
Defect associated with bleeding	No	Occasional But doubtfull	In two cases administration of plasma or whole blood has stopped the bleeding manifestation. (Ref.7-9)
Defect associated with thrombosis	No	Possible	Especially M.I.
Defect associated with hypertension	Rare	Often	

4. Patients and Methods

4.1. FXII deficiency

Patients with FXII deficiency have been gathered from two sources: 1) personal files which referred to the patients with this deficiency seen in Padua during the past 50 years, and 2) from four, time unlimited, Pub Med searches carried out on march 2003, June 2005, April 2016 and June 2018.

For cases studied before 1983, we refer to the data gathered by Prof Ratnoff's group [11]. All papers published on this coagulation disorder since that excellent review have been evaluated. A few papers published before 1983 and which were not included in Ratnoff's group paper were now also taken into due consideration. The Pub Med search was carried using the following keys: FXII and thrombosis; FXII and bleeding; contact phase deficiency and thrombosis. Original papers, regardless of the language, were obtained with the collaboration of the Pinali Medical Library of Padua Medical School. Only cases with proven congenital deficiency were taken into consideration. Besides specific factor activity, corresponding antigen levels were also recorded, whenever available. When dealing with a case deficient in one of these factors, the levels of the other proteins of the contact phase were also recorded, whenever available. Molecular biology studies were reported whenever available. Inclusion criteria were:

1) Specific factor activity of less than 15% of normal; antigen levels, on the contrary, could be variable.

2) Compatible hereditary pattern with at least one homozygote or a documented or presumed compound heterozygote in the family.

3) Exclusion of patients with a concomitant coagulation defect.

4) Exclusion of circulating anticoagulants and/or antiphospholipid syndrome.

5) Exclusion of circulating anticoagulants and/or antiphospholipid syndrome. Thrombotic events had to be demonstrated by objective methods (sonography, venography, pulmonary scintiscan, electrocardiogram, cardiac enzymes elevation, computerized axial tomography etc.).

All cases which did not meet the above mentioned criteria were excluded from the final computation. The presence of associated diseases was recorded for every patient. Since a few patients had more than one associated disease, for the purpose of the present study only the condition of the "present illness" was taken into consideration.

a) Prekallikrein deficiency

Patients with Prekallikrein deficiency were gathered from three sources: 1) two, time-unlimited, PubMed searchs carried out on January 2010 and March 2018. Several Keywords, including the Mesh terms supplied by PubMed were used. Side Tables were also evaluated whenever available 2) Personal files pertaining to patients with proven PK deficiency 3) Cross checking of the references listed at the end of each paper. Original papers, regardless of the language, were obtained with the help of the Pinali Medical Library of our University. Only papers dealing with case series studies, case reports and case reviews were considered. Papers with acquired PK deficiency were excluded. Inclusion criteria were a sure or highly probable congenital PK deficiency based on 1) a prolonged aPTT together with a normal PT corrected by normal plasma or serum 2) Low PK levels (less than 15% of normal, 3) shortening of aPTT on long incubation times 4) normal FXII and FXI. PK antigen assay and molecular biology diagnosis were recorded but were not considered a sine qua non condition

for inclusion. This was due to the fact that only a small minority of patients could meet these two last criteria.

The presence of associate diseases was recorded as listed for FXII deficiency. Also in this case thrombotic events had to be documented by objective methods.

5. Results

5.1. FXII deficiency

In 1983, Ratnoff's group dealt with 120 cases of FXII deficiency [11]. The diagnosis in all these patients had been confirmed directly or indirectly in their laboratory. Our personal files, a Pub Med systematic search and cross-checking of the references listed at the end of the single papers yielded 111 additional cases of FXII deficiency including the large Swiss series [5] bringing the total, for the FXII deficiency, to 231 [12-16].

In recent years, 15 additional cases have been reported or recognized bringing the total number to 246 [17-30]. There was no case with a combined defect of the two factors. The male-female ratio was about 1 but in the studies with series of patients, gender was not specified [11].

The number of patients with FXII deficiency with thrombotic events as reported by Ratnoff's group were 32 (16 arterial; 16 venous) [11]. Since five additional cases of FXII deficiency and thrombosis (3 arterial and 2 venous) have been gathered by us in the last few years [26-30], the total number is now 37 (19 arterial and 18 venous) out of the 246 reported cases. Hypertension was rare. Overall the most frequent thrombotic manifestation were M.I., DVT with or without PE (**Figure 1**). Associated congenital risk factors were present in three patients (1 heterozygous and 1 homozygous FV Leiden defects and 1 heterozygous antithrombin deficiency). Acquired risk factors (diabetes, hypertension, trauma, obesity etc...) were present in 31 cases. In three cases, no associated risk factor was present. In the remaining patients no data were supplied in this regard.

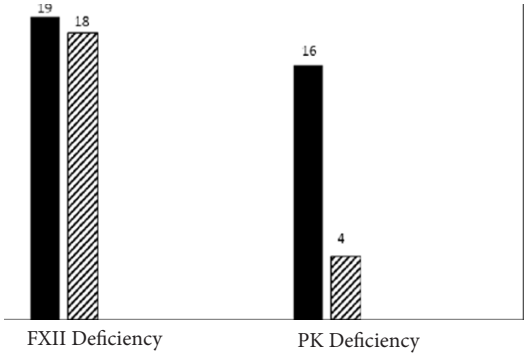

Figure 1: Number of thombotic events reported in patients with FXII or PK deficiency, (Factor level less than 15O of normal). The dark histograms refer to arterial thrombosis while the hatvhed ones refer to renous thrombosis. The total number of patients reported or investigated were 246 and 106 for FXII deficiency and for prekallikrein deficiency respectively.

6. Discussion

Nobody knows the exact number of homozygous or compound heterozygous patients with FXII or Pre kallikrein deficiency, existing in the world. The only figures available are those referring to reported cases. However this is also only approximate since it is likely that cases reported in some languages and in local journals go undetected. Finally, it is likely that these asymptomatic patients remain unreported unless a co-morbidity is present. As a consequence of the above it is clear that the figures here presented are only orientative and biased but they are the only ones, despite the limitation, on which a discussion can be generated.

It is interesting to note that no proven case of combined deficiency of FXII and PK has ever bee reported.

There are occasional reports of PK deficiency with slightly decreased or borderline low FXII, but not cases of severe concomitant deficiency [6].

Since FXII and PK defect are rare but not particularly rare, it is surprising that no combined defect has ever appeared. Granting for some omissions due to our fault it may be estimated that at least about 250 cases of FXII deficiency and about 125 cases of PK deficiency have been reported in the world literature. Furthermore, due to the lack of symptoms, it is likely that many cases went and still go undetected and unreported.

The most striking difference between these two defects regards the relation with hypertension (**Figure 2**).

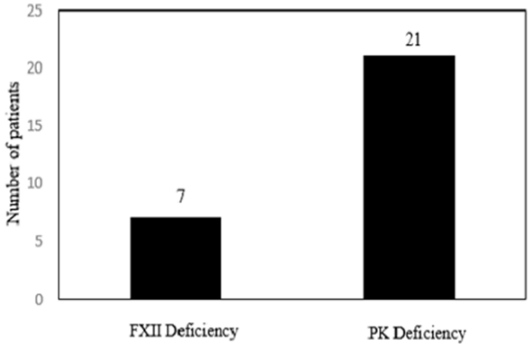

Figure 2: Hypertension reported in patients with congenital deficiency of FXII and of PK. The reference numbers are 246 and 106 for FXII and PK respectively.

There are few reports of hypertension in patients with FXII deficiency. On the contrary, hypertension and its complication have been frequently found in PK deficiency [33,34].

It is known that administration of ellagic acid, a potent FXII activator, in animals is associated with with a sharp shortening of clotting time in silicone coated tubes, a drop in blood pressure and consequent decrease in post surgical (tail section) bleeding [42,43]. The shortening of clotting times was seen also in humans [44].

This could be interpreted as the result of maximal activation of PK, a vasodilator [1,34].

The number of cases with FXII deficiency was reported to be 120 in 1983 [11] and 231 in 2011 [15,16]. At present it can be calculated at around 246 cases.

On the contrary, PK deficiency was estimated at 38 cases in 1983 [11] and at 73 cases in 2010 [6]. Today the number of sure or highly probable reported cases has reached 106 [34].

Needless to say, these figures are only orientative since many cases surely went and still go undetected for the lack of symptoms.

The patients who present an associated condition or comorbidity are probable more frequently reported creating and evident bias. However since these are the only data available we have, even though with sure limitations, to work with these numbers.

From these data it would seem that FXII is twice more frequent than PK deficiency. Whether this is true or it is only due to the fact that FXII deficiency has been reported about 10 years earlier (1955) as compared to PK deficiency (1965) [35] or it reflects a real difference in prevalence, remains to be proven.

It may be stated that cardiovascular conditions are equally present in both FXII and PK deficiency even though hypertension seems more frequent in PK deficiency. As far as bleeding is concerned, there are two cases of documented and unexplained bleeding in patients with PK deficiency but no case in FXII defect.

The bleeding in two patients with PK deficiency has been demonstrated to recede or stop after plasma or whole blood transfusion [7,9]. This suggests the likelihood of a correction of a defect.

This survey of all available cases of FXII or PK deficiency may be useful in the attempt to clarify the clinical significances of these defects. The result of the study are in sharp contrast with the results of the experimental studies in mice which indicate a prothrombotic effect of these factors with consequent suggestion that anti-contact phase compounds could be useful in protecting from thrombosis [45-48]. Clinical observations in congenital deficient patients do not confirm this hypothesis [49]. Both patients with FXII deficiency and, particularly, those with PK deficiency may present M.I. and venous thrombosis.

In the past, FXII deficiency was even considered to be a risk factor for thrombosis. Now this has been demonstrated not to be the case. However this hypothesis is still open for PK deficiency [6,33].

In any case it may be stated that patients with a severe deficiency of these two defects neither cause thrombosis nor represent a protection from thrombotic events. An exception to this second part of this statement may be conceived for Pre kallikrein deficiency due to the frequent presence of hypertension seen in this condition [6,33].

7. Compliance with Ethical Standards

1. The study was performed according to the Helsinki convention and its ethical standards.

2. No conflict of interest. None of the Authors have received grants or compensation.

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