

Comparison between Congenital Prekallikrein Deficiency in Humans and Animals

Girolami A*, Cosi E, Ferrari S, Lombardi AM, Girolami B

Department of Medicine, University of Padua Medical School, Via Ospedale, 105, Padua, 35128, Italy

ABSTRACT

Objective: To compare the effects of congenital Prekallikrein deficiency in humans and in animal.

Patients and animals: All reported cases of patients with Prekallikrein deficiency have been taken into consideration as gathered from personal papers and Pub Med repeated searches carried out during the past 16 years. Prekallikrein deficiency in animals has been obtained by two Pub Med searches carried out on July 2017 and May 2018.

Results: Congenital Prekallikrein deficiency in humans is associated with no bleeding tendency even though in two patients surgical bleeding has been reported to stop after the administration of Fresh Frozen Plasma.

Bleeding in animals was seen in one horse after castration and in a dog with unexplained gastrointestinal bleeding

Hypertension, hypertension related disorders and thrombosis have been frequently reported in humans with Prekallikrein deficiency. On the contrary no cardiovascular disorder or thrombotic event has ever been reported in Prekallikrein deficient animals.

Conclusions: Comparison between human and animals has a limitation due to the fact that the number of animals with such a defect is very scanty. Due to the revival of interest in the contact phase of blood coagulation it would be very useful if a large number of animals, dogs in particular, could be investigated. Such study could cast some new light on the relation between the contact phase of blood coagulation and cardiovascular diseases and thrombosis.

Key words: Prekallikrein deficiency; Humans; Animals; Bleeding; Thrombosis; Cardiovascular diseases

INTRODUCTION

A similar study in humans is of difficult realization because of the rarity of the condition. The contribution of animals to the study of blood coagulation is not trifle. Animals with a bleeding tendency belong to two categories, namely to 1) natural type and 2) knockdown genetic chimeric forms [1]. Most coagulation experts are familiar with hemophilia A or hemophilia B occurring in animals, usually dogs or mice. Animals with rare coagulation disorders are less known. Little is known about the relationship existing between humans and animals with regard to non-hemorrhagic clotting disorders such as FXII deficiency or PK deficiency [1]. This is so despite the fact that a few species of animals have been reported to have these defects [2-10]. The purpose of the present study is to investigate and compare the PK defect of humans with that of animals. The discussion will involve only natural cases with PK deficiency. Chimeric animals will be disregarded. The rationale

of the study is justified on one hand by the present day revival of the interest on the contact phase of blood coagulation [11-14]) and also by the recent investigations, in humans which suggest that cardiovascular diseases are frequently encountered in patients with congenital PK deficiency [15-18].

MATERIALS AND METHODS

106 patients with proven or highly probable congenital PK deficiency were examined. Proven cases were those who were investigated by molecular biology techniques. Unfortunately, these patients are so far only twelve [18]. The highly probable cases were those who were diagnosed on the basis of clotting tests. The clotting tests had to meet the following criteria

- Prolonged PTT
- Full correction by the addition of normal serum or plasma

Correspondence to: Girolami A, Department of Medicine, University of Padua Medical School, Via Ospedale, 105, Padua, 35128, Italy. Tel: 00390498213026, Fax 0039049657391 E-mail: antonio.girolami@unipd.it

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- Low PK level with normal FXII and FXI levels
- Progressive shortening of the PTT on long incubation times.

All papers dealing with PK deficiency in animals were gathered by two times unlimited PubMed search carried out in July 2017 and in May 2018 [15]. All cases were included. Genetic analysis was reported for only one animal [1-7]. The animal shown to have congenital PK deficiency is rats, dogs, and horses. The presence of bleeding was recorded in every instance both for humans and animals. The same was true for the presence of cardiovascular disorders and thrombosis (Table 1).

RESULTS

12 patients with PK deficiency were investigated by molecular biology techniques. The great majority of cases were included on the basis of clotting tests. The mutations detected, involved several exons, but mainly exon 14 (five cases). Twenty patients with PK deficiency showed the presence of cardiovascular disorders (arterial or venous) [18]. Several of these patients have associated risk factors as hypertension and dyslipidemia. On the contrary bleeding was reported only in a few cases [15]. A total of 17 animals were reported to have Prekallikrein deficiency [2-8]. Molecular studies were carried out only in one instance for a dog that resulted to be homozygous for the Phe330Ile mutation [4]. Among animals, bleeding was reported in only one case (horse) after castration [6]. No cardiovascular abnormality or venous thrombosis was ever reported in any animal with PK deficiency [2-8] (Table 2).

DISCUSSION

PK deficiency in humans is not associated with bleeding. The few episodes of bleeding reported in PK deficiency do not withstand a critical analysis [15]. They were likely to be due to associated, unknown causes or were accidental events which occurred in patients with PK deficiency. An incomplete or a wrong diagnosis, could also involve [15]. In only two patients with PK deficiency

the administration of plasma stopped or decreased the bleeding [19,20]. On the contrary, cardiovascular disorders have been frequently discovered in patients with PK deficiency [15-18]. In animals, bleeding has been observed in a horse after castration [6] and in a dog that presented gastrointestinal bleeding [8] unfortunately no thorough investigation was carried out in these two animals. This observations, altogether, seems in agreement with what seen in humans. On the contrary, no thrombotic or cardiovascular disorders, has been discovered in animals with PK deficiency. Needless to say that no absolute significance can be given to these findings due to the differences in diet, behavior, associated diseases, life habits, observational techniques, follow up etc. However, it would seem safe to suggest that PK deficiency is potentially more dangerous in humans than in animals. Since no long term observational study of PK deficient in dogs or other animals is available, unfortunately, no strict comparison can be carried out. PK deficiency seems rare in animals.

CONCLUSION

In a review on coagulation defects seen in animals, PK deficiency is not mentioned. Even FXII deficiency seems rare in dogs as compared to Hemophilia A or Hemophilia B. It is interesting to note that a mild bleeding tendency was reported in a patient who showed PK deficiency together with partial FXII defect [21]. In this regard, a similar observation was reported in a dog that presented gastrointestinal bleeding [8]. This could indicate that the combined severe deficiency of FXII and PK, namely the deficiency of the two main factors of the contact phase could cause bleeding. Unfortunately, there is no reported case of a severe concomitant deficiency of FXII and PK neither in humans nor in animals and therefore no conclusions can be drawn. The similarities found between the PK defect in humans and animals indicate that phylogenetically the contact phase system is the same. It confirms the lack of bleeding. Because of the present time revival of interest in the role of the contact phase of blood coagulation in the pathogenesis of cardiovascular disorders (11-14), observations in animals, besides humans, would also be important. Unfortunately, there is no observational study about the incidence of cardiovascular disorder in animals (dogs in particular). Animals with PK deficiency have only been investigated at the time of the diagnosis of the defect or for a short time thereafter. This impedes the comparison with the observations made in humans. Humans have been often followed for several years even though no long term, adequately controlled, observational study has ever been carried out even in humans. The rarity of the defect among humans together with the fact that these patients are often undetected since they are asymptomatic prevents the gathering of an adequate number of patients. A parallel study in a colony of affected dogs or other animal could supply useful information with regard to the role played by PK deficiency and hypertension, hypertension related diseases and thrombosis. The study should concern PK deficient animals since it has been demonstrated in humans that FXII deficiency does not cause cardiovascular disorders and thrombosis [22-24].

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Table 1: Animals with proven hereditary PK deficiency

Authors (year)	Animal	Comments
Damas J et al. (1980)	Rat	-
Turrentine MA et al. (1986)	Horse	-
Chinn DR et al. (1986)	Dog	Several species of dogs are included

Table 2: Bleeding and Cardiovascular disorders reported in humans and animals

Patients or animals	Total number	Bleeding	Cardiovascular disorders and thrombosis	Comments
Patients	106	2	29	Bleeding stopped after administration of fresh frozen plasma
Animals (Dogs, horses, rats)	17	2	None	A horse showed bleeding after castration; a dog showed unexplained intestinal bleeding.

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