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Higher prevalence of arterial vs venous disorders in patients with congenital Prekallikrein deficiency

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Congenital PK deficiency is one of the contact phase defects of blood coagulation.

The other two are represented by FXII and Kininogen (K) deficiencies [1].

The condition has been drawing considerable attention during the past few years. The first review article on the subject appeared in 2010 and dealt with a literature of about 90 patients [2]. Several additional cases have been reported in the following years [3-9].

The most striking aspect of Prekallikrein (PK) deficiency consists in the discrepancy between the severe coagulation defect and the paucity of its clinical manifestations. Bleeding was occasionally reported but it seems to be unrelated to the clotting defect [2].

Patients with PK deficiency show often with hypertension and hypertension related disorders [10,11].

An evaluation of the 121 cases of PK deficiency so far reported [1,5-9] indicates that 25 (20,66%) of them showed arterial diseases (hypertension or its complications) whereas only 4 (3.31%) had venous disorders (thrombosis). The difference between arterial and venous disorders is clear and is statistically significant (p=0.01) (Table 1). Three of the patients with Venus Thrombosis (V.T.) had also hypertension. The other had pulmonary embolism (P.E.) and an ischemic stroke [12,13]. The latter is the only patient who had both an arterial and a venous thrombosis [13].

The discrepancy between arterial and venous thrombosis is important since it suggests that, at least in some instances, the events may be two different conditions.

These findings are in agreement with the following observations:

1. PK deficiency is common among African Americans (AA) and apparently among Africans [14].
2. African- Americans present often hypertension and hypertension related disorders [15-17]. The same may be true for Africans but this has not been demonstrated yet.
3. PK deficiency has been less frequently demonstrated in Caucasian-Americans [14].

The main physiological roles of PK is to reinforce the activation of FXII and to release bradykinin from High Molecular Weight (HMW) kininogen [1].

These results indicate that the pathogenesis of thrombus formation is different in arterial and in veins. The status of the vessel wall is important in arterial diseases whereas the coagulability of blood plays a major role in venous thrombosis.

The lack of bradykinin formation due to the lack of PK seems deleterious mainly for the arterial wall function. Hypertension may occur.

Protracted hypertension leads to atherosclerosis and to arteriosclerosis. The former predisposes to atheroma formation. The atheroma may fissure or ulcerate and cause local activation of coagulation with fibrin deposition and thrombus formation. Occlusion of the arterial vessel may ensue.

Since hypertension is frequent among African Americans it is conceivable that the co-existence of PK deficiency may play a role. This is suggested by the frequent presence of PK deficiency among African Americans [14].

This observation confirms that PK acts also on the arterial wall and not only on the clotting mechanism. It is commonly accepted that arterial thrombosis is mainly associated with athero and arterialsclerosis whereas venous thrombosis is mainly dependent on blood coagulation. However, this may not be absolute since at least one patient showed both arterial and venous thrombosis [13] and in at least another family, two affected siblings presented arterial or venous thrombosis [12].

Finally, it is worth noting that 9 of these patients (36,0%) were African-Americans (AA).

This figure is higher than expected just for this population of the USA (42 million out of 380 million) namely 11,05%. Furthermore, it has to be noted that the ethnic background of USA patients with this clinical condition is not always indicated; it is likely, therefore, that the proportion of AA would be further increased [13,18-19].

The frequent presence of Prekallikrein deficiency found among African-Americans may, at least in part, justify the high prevalence of cardiovascular disorders seen in this ethnic population [15-19]. Needless to say that other factors such as diet, type of work and environment may play a role. A close relation between some PK gene polymorphisms and hypertension has been demonstrated also in other populations [20].

This observation further supports the likely role of Prekallikrein deficiency in the pathogenesis of arterial hypertension and related disorders and indicates also that venous thrombosis is rare in this defect.

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Table 1. Main features of patients with prekallikrein deficiency and venous thrombosis

Authors (year)	Age/ gender	PK Activity (%)	PK Antigen (%)	Type of defect	Degree of hypertension	Other associated risk factors	Complications of hypertension	Comments
Goodnough, et al. 1988 (12) Case 1 Case 2 Case 3	 M, 42 F, 36 F, 44	 1 1 1	 Absent Absent Absent	Probably Hom. Same Same	 n.r. n.r. n.r.	 none obesity obesity	 Stroke n.r. n.r.	Patient had alsoPE Patient had DVT Patient had DVT+PE; The three cases were siblings
Girolami, et al. 2018 (11)	M, 53	1	90	Comp Het.	Severe	Hypercolesterolemia	none	T insertion,+ Asp558Glu mutation; DVT. A brother had two M.I.

DVT= deep vein thrombosis; PE= pulmonary embolism; Hom=homozygote; References number between parenthesis.

Conflicts of interest

The authors declare that they have no conflict of interest.

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