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Homozygous Prekallikrein Deficiency in the USA: Several Patients but Still Few Mutation Studies

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Prekallikrein (PK) deficiency was first reported in the USA by Hathaway et al. in 1965.[1] The defect was a new asymptomatic condition despite the presence of a prolonged Partial Thromboplastin Time (PTT). After that description several cases were reported but the defect never stimulated a widespread interest.

The total number of reported cases in the USA is about 60.[2-4] However, some of these were just listed as cases and no medical history was supplied.[2] It is also likely that some of these cases were subsequently reported as case studies.[3] The aim of this Letter is to call the attention of the readers to the fact that up to now only a few patients with this disorder have been investigated by molecular study.

Literature Review

PK is one of the contact phase of blood coagulation. Its main functions are: 1) liberation of bradykinin from High Molecular Weight Kininogen, 2) contribution to FXII activation, 3) stimulation of fibrinolysis.[5]

The number of patients with PK deficiency who have been presented in full papers is about 40.[4]

Recently, an increased interest in the defect was stimulated by the observation that Cardiovascular Disorders (CVD) were frequently present in the patients who carried the defect.[6] The CVD disorders were represented by hypertension and its complications.[6]

There is also a discrepancy between the number of case reports and the paucity of genetic studies.

Up to now only 2 cases of PK deficiency have been studied in the USA by molecular techniques. The first patient, an African-American (AA), has been studied in 2009 by Dasanu et al., and found to have a Cys529Tyr defect.[7] This mutation is actually Cys548Tyr since, originally, the prepro section of the molecule was not counted.

The other mutation seen in another AA is Ser151Phe fs. The latter mutation was recently confirmed by Adenauer et al.[8] in a patient described in Texas by Dasgupta et al. 2020.[9] The mutation in the latter patient was originally reported as Cys97Tyr fs Ter 173.[9]

Since PK deficiency is frequent in the USA, particularly among AA[3,4] it is surprising that no other patient underwent a genetic study.

On the basis of the 2 cases available, it seems that more than one mutation is responsible for the genetic makeup of Prekallikrein deficiency among AA. It is likely that Caucasian-Americans with PK deficiency could carry different mutations.

The origin of the patient presented by Dasanu et al.[7] is Jamaican-American. The second patient probably comes from Nigeria since it has the mutation Ser151Phe fs recently described as frequent in that country.[8] Since the Africans who were forcefully brought to the USA and to other American countries originated from Nigeria and other West Africa States it is likely that these 2 mutations could be frequently found among AA.

Since the West Africa states represent a variety of populations; it is likely that other mutations will be found in the USA and in other West Africa States.

The idea that only the Ser151Phe fs mutation could be at the basis of the large AA population (42 million) of the USA seems unlikely.

It is surprising that no other mutation has been so far discovered. No patient in the USA, besides the ones presented by Dasanu et al.[7] and by Dasgupta et al.[9] have been reported.

This is probably due to the fact that the PK defect has drawn and still draws little attention because affected patients do not bleed.

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Conclusions

The recent studies which have shown that the defect may play a role in arterial disorders will probably modify this attitude and stimulate genetic studies of the AA population. Unfortunately, the structure-function studies on PK deficiency are still limited and no conclusion can be drawn.[8,10,11]

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