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Myocardial Infarction and Arterial Thrombosis in Severe (Homozygous) FXII Deficiency: No Apparent Causative Relation

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Summary: Twenty-one patients (12 female and 9 male) with severe (homozygous) factor XII (FXII) deficiency and 58 (32 female and 26 male) with heterozygous FXII deficiency were observed for an average 16.2 years. No patient with homozygous FXII deficiency experienced myocardial infarction or any other arterial thrombosis. The same was true for heterozygotes. The cases of FXII deficiency and arterial thrombosis reported in the literature were evaluated. In every instance, associated risk factors were present that could justify the arterial thrombosis. Dyslipidemia, hypertension, smoking, and diabetes mellitus were the most frequent findings. The examination of the few papers that dealt with the prevalence of arterial thrombosis in patients with severe FXII deficiency showed that only 1 patient of 61 experienced myocardial infarction. In conclusion, it seems that the role of FXII deficiency in the pathogenesis of arterial thrombosis is minor.
Key Words: Coagulation—Arterial thrombosis—Factor XII deficiency—Contact phase.

Factor XII (FXII) deficiency, first described in 1956 by Ratnoff and Colopy (1), is a peculiar condition in which there is a discrepancy between laboratory tests and the clinical picture. In fact, the activated partial thromboplastin time is severely prolonged but patients are asymptomatic.

FXII deficiency had been described as a "hemorrhagic condition" (1). Subsequently it was seen that this was not the case (2–4). The death of Hageman due to pulmonary embolism has stimulated an interest about the potential role of the contact phase of blood coagulation in the pathogenesis of venous or arterial thrombosis (5–10).

The main purpose of this study is to report the incidence of myocardial infarction in the several-year follow up of 21 homozygotes and 58 heterozygotes with FXII deficiency. The second purpose was to analyze all cases of myocardial infarction or other arterial thrombotic manifestations seen in patients with FXII deficiency and reported in the literature to ascertain if associated risk factors were present in these patients at the time of the thrombotic insult.

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MATERIALS AND METHODS

All 21 patients seen by us during the previous 35 years and diagnosed to have severe (homozygous) FXII deficiency were included in the study. The criteria for diagnosis were 1) very low levels of both FXII activity and antigen (less than or equal to 1% of normal, and 2) presence of a heterozygous defect in all parents and children of the propositi. The criteria for inclusion for the heterozygote group were 1) presence of at least 1 homozygote in the family, 2) parents or children of homozygotes, and 3) presence of at least 2 other heterozygotes in the family when no homozygous patient was present in the family. After diagnosis, all homozygous patients were observed by us on a regular basis at least every year. Twelve patients were female and 9 male. The average follow-up period was 16.2 years

(range, 3–35 years) for a total of approximately 360 patient/years. The heterozygous subjects were observed less regularly. Often information was gathered indirectly from the homozygous family member or by the caring physician.

All sporadic or anecdotal reports of myocardial infarction or other arterial thrombosis occurring in patients with severe FXII deficiency have been gathered and analyzed (6,8,11–20).

The few papers dealing directly or indirectly with the prevalence of myocardial infarction or other arterial thrombosis in patients with severe (homozygous) FXII deficiency have been also evaluated (9,20–22).

Routine coagulation tests were carried out as previously reported (23). FXII assay was carried out as previously reported using a known FXII congenitally deficient plasma as substrate and an ellagic acid activated partial thromboplastin (3).

FXII antigen measurement was carried out by means of an electroimmunoassay as previously reported (24,25). The antiserum, supplied by Behringwerke, Marburg, Germany, was mixed with agarose at a concentrate of 5%. The migration time was 5 hours at a potential difference of 10 V/cm.

Antithrombin, protein C, and protein S were evaluated as previously reported (26). FV Leiden and G-to-A 20210 prothrombin polymorphisms were studied both from a clotting and a genetic point of view according to accepted procedures (27).

RESULTS

No myocardial infarction was seen in the patients observed for an average of 16.2 years (range, 3–35 years). The total observational period for the homozygote patients was approximately 360 patient/years. The occasional presence of mild-to-moderate associated risk factors was seen in some of these patients. Smoking, always light or moderate (less than 20 cigarettes/day), was present in 4 patients. Mild-to-moderate hypertension was present in 3 patients. Type II diabetes mellitus was present in 1 patient; dyslipidemia was present in 2 patients. A few patients had more than 1 risk factor. However, none of these risk factors appeared particularly important in any of our patients; for example, no type I diabetes mellitus was present.

Twenty homozygote patients had no associated congenital prothrombotic conditions. One patient, a female, had a FV Leiden polymorphism at the heterozygote level (24).

The review of the literature revealed 10 reported cases with myocardial infarction or arterial thrombosis in patients with severe FXII deficiency (Table 1). No long-range follow-up was available for any of these patients.

The analysis of these 10 cases revealed that in most patients there were important associated risk factors that could by themselves be responsible for the vascular complication (Table 2). Hypertension and/or dyslipidemia were present in most cases.

TABLE 1. Cases of Myocardial Infarction in Patients with Severe FXII Deficiency

Author	Year	Age and Gender	No. of Cases	Type of Arterial Thrombosis	Associated Risk Factors
McCain et al. (12)	1959	59, M	1	Thrombotic CVA	Hypertension
Glueck et al. (15)	1966	19, F	1	M.I.	Hypertension, diabetes
Hoak et al. (16)	1966	59, M	1	M.I.	Dyslipidemia
Egeberg (11)	1970	72, M	1	CVA (type unknown)	Hypertension, diabetes
Walsh (17)	1970	?	1	M.I.	No data
Vroman (14)	1976	?	1	M.I.	No data
McPherson et al. (13)	1977	55, M	1	Femoral thrombosis	Atrial fibrillation, elevated FVIII
Goodnough et al. (6)	1983	52, M	1	M.I.	No data (two brothers showed both FXII deficiency and diffuse atherosclerosis)
Hellstern et al. (8)	1983	32, M	1	Femoral thrombosis	Smoking, dyslipidemia, Burger's disease
Lodi et al. (14)	1984	40, M	1	M.I.	Borderline BP

TABLE 2. Myocardial Infarction or Arterial Thrombosis in Series of Patients with Homozygous (Severe) FXII Deficiency

Author	Year	No. of Cases	No. of MI or Other Arterial Thrombosis	Age and Gender	Associated Risk Factors
Sinkos et al. (29)	1967	2	0	—	n.a.
Schved et al. (20)	1988	2	0	—	n.a.
Rodeghiero et al. (19)	1991	18	1	51, M	No data available
Lammle et al. (9)	1991	18	0	—	n.a.
Present paper	2003	21	0	—	n.a.
Grand Total		61	1	—	n.a.

n.a., not applicable; MI, myocardial infarction.

Furthermore, in every instance, myocardial infarction and other arterial thrombosis occurred, with only 1 exception, in middle age men who are commonly known to have an increased risk of arterial thrombotic diseases. Finally none of these patients were investigated for the presence of associated thrombotic conditions.

The few papers that dealt with the incidence of myocardial infarction or arterial thrombosis in patients with severe FXII deficiency indicate that only 1 myocardial infarction was seen in 61 patient reported. This was a 51-year-old man for whom, unfortunately, no further data are supplied (25).

DISCUSSION

FXII deficiency is not, in comparison to other clotting disorders, a rare disorder. At least 200 cases have been reported while many other surely went undetected and unreported because patients did not show any clinical manifestations of disease.

The description of the death of Hageman due to a pulmonary embolism after a hip fracture has had a vast resonance (3). Immediately thereafter, several authors have described patients with the Hageman trait and several and variable venous or arterial thrombotic manifestations. All these sporadic reports failed to recognize the limits of their findings and often drew conclusions that were unjustified. Lack of adequate controls, limited value of anecdotal reports, and failure to investigate properly the possible presence of congenital prothrombotic state in the propositi should have been taken into consideration. Possible associated acquired risk factors were often disregarded.

It is often difficult to resist the wish to attribute a pathogenetic significance to a given finding, disregarding all the rest.

Because all homozygous patients who showed a myocardial infarction or an arterial thrombosis also had other acquired conditions known to facilitate thrombosis, it is likely that the association was coincidental. Furthermore, because most patients were not investigated for the presence of associated congenital conditions, the possibility of a coexistence of 1 of these conditions cannot be excluded. FV Leiden or G-to-A prothrombin polymorphisms are present in approximately 3% to 6% of the general population (28,29). Finally some of the case reports seem quite "stretched." Typical of this is the patient reported by McPherson and colleagues (13) who was claimed to have had a femoral artery thrombosis because of the FXII deficiency, even though atrial fibrillation was present. The patient of ours, who had associated FV Leiden polymorphism, presented venous thrombosis but no arterial thrombosis (25).

The occasional report of arterial thrombosis in partial deficiency (heterozygosity) seems even more likely to be only the expression of a chance association (9,30–32).

Recently it has been demonstrated that the claim that FXII is associated with an increased risk in venous thrombosis is untenable (30). The thrombosis appeared to be due either to an associated known risk factor or to be a chance association. In agreement with these results, in the Leiden thrombophilia study there was no difference in FXII level between patients with thrombosis and subjects without thrombosis (32).

None of these patients with myocardial infarction or arterial thrombosis underwent autopsy, so no demonstration of a thrombus has ever

been obtained. In 1 case, there was radiologic evidence of coronary thrombosis (19). The only known autopsy reports are those obtained from Hageman, who showed not only pulmonary embolism, but extensive atherosclerosis (5).

The few studies that have investigated the incidence of arterial thrombosis in patients with severe FXII deficiency have also failed to show significant data. Only 1 of 61 patients had a myocardial infarction. The present observation has the additional value of having the result of a long-term follow-up of all the 21 patients being investigated.

On the basis of the present observation and on the basis of those that have excluded the existence of a relation between FXII deficiency and venous thrombosis (30–33), it seems justified to conclude that FXII deficiency plays no sure role in the pathogenesis of thrombotic phenomena. It may be only concluded, as correctly already stated by Ratnoff, that Hageman trait does not offer protection from thrombosis despite the great prolongation of the partial thomboplastin time (5).

The possibility that FXII deficiency, in association with other congenital or acquired conditions, under special circumstances, could play a role in the pathogenesis of the thrombotic complication seems unlikely but cannot be completely excluded. A coagulation alteration found in a thrombotic patient cannot be immediately maintained to be the cause of thrombosis. All papers dealing with the subject appear to have jumped to unjustified conclusions. This is particularly so when one deals with a complex condition such as coronary artery disease. Finally, occasional arterial thrombosis has been reported for other contact phase factors deficiencies, for example, prekallikrein (34).

Recent studies on the relation between FXII polymorphism or other gene alterations and thrombosis are not univocal and do not modify the previously mentioned conclusions (35–37). As a matter of fact, they may support them because it has been shown that homozygosity for the 46 C-to-T polymorphism is associated with decreased FXII levels and an apparent protection from coronary artery disease. Therefore low levels of FXII seem to offer protection from thrombosis and not cause thrombosis (35,36). Recent emphasis on levels of circulating activated FXII as a possible marker for thrombosis is also equivocal (7,10). For example, some authors found a positive correlation between levels of activated FXII and serum cholesterol, smoking, body mass index, hypertension, and number of stenosed vessels on angiography (38,39). Others found that in patients who survived myocardial infarction, activated FXII levels were higher than those in controls. This could be interpreted in two ways. First, it could be, as the authors surmise, that the increased levels of FXIIa were the cause of myocardial infarction. Conversely it could be that patients with increased levels managed to survive the myocardial infarction. In fact FXIIa stimulates, among other activities, endogenous fibrinolysis. Furthermore it has to be remember that massive activation of FXII by infusion of ellagic acid in dogs and also in humans caused a clear hypercoagulable state but no thrombotic manifestation (40,41).

The proposal to include FXII or FXIIa assays in the battery of prothrombotic tests formulated some time ago by some authors is not justified (42). By doing so, no benefit is obtained for the patient; on the contrary, it may represent only an increase in medical costs.

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