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State-of-the-Art Review

Low Incidence of Venous Thrombosis in Homozygous Patients with NT 20210 G to a Prothrombin Polymorphism

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A few years ago it was stated that a prothrombin polymorphism, the nt 20210 G to A alteration, was associated with increased levels of prothrombin and an increased incidence of venous thrombosis (1). The significance of this association remains doubtful. There is a widespread, although not unanimous consent, about the existence of a mild association of this abnormality with venous thromboembolism (2–6). However, there are conflicting studies as to the importance of this prothrombin abnormality in the pathogenesis of arterial (cerebral, coronary) thrombosis (7–9). We thought that a careful evaluation of the prevalence of venous thrombosis in all homozygote patients so far described could be useful in understanding the impact of the defect on phenotypic manifestations.

MATERIALS AND METHODS

All available papers dealing with the Nt G to A prothrombin polymorphism have been examined by two independent investigators (1–6,10–15). Patients were allocated to the homozygous state according to the data presented in the paper. Genetic analysis was compared with family pedigree when available. Heterozygous patients were not included. All patients were classified as symptomatic or asymptomatic. Only deep vein thrombosis was taken into consideration. Conclusions were compared, and if concordant, entered as final. In case of discrepancies, a third investigator studied the paper, and the patients were assigned to the symptomatic or asymptomatic group according to the latter investigator.

RESULTS

A total of 18 patients shown to be homozygous for the abnormality have been reported so far (Table 1). Some of these patients have been reported to be symptomatic, others asymptomatic. Six patients were female and 11 patients were male. In one instance the sex of the patient was not specified (15). The age varied between 18 and 72 years. In two cases, the age of the proposita was not specified (1,15).

In one instance the patient remained asymptomatic even after a long period on oral contraceptive therapy (4). In another there was no thrombosis despite two surgical procedures (5). The first case reported was symptomatic, but there was a concomitant FV Leiden defect (1). Furthermore it was not specified whether or not associated acquired risk factors were present. One additional patient showed a concomitant congenital (factor V Leiden) and an acquired prothrombotic condition (immobilization) (10). Another patient was symptomatic but showed a concomitant congenital defect, hyperomocysteinemia (2). Altogether, three of the symptomatic patients had a concomitant congenital prothrombotic condition (two had factor V Leiden and one had hyperhomocysteinemia) and one also had an acquired condition (immobilization). Therefore they cannot be fully accounted for.

Three additional symptomatic patients had important concomitant acquired conditions (pregnancy, 2 and surgery, 1), and therefore they appear doubtful (11,12,14). If these doubtful or complex cases, for a total of 6, are eliminated one comes to the conclusion that only 4 of the original 18 homozygous patients showed idiopathic venous thrombosis apparently associated only with the prothrombin abnormality (3,13,14). This is a small number for a homozygous state. Altogether, 8 of 15 patients with only the prothrombin abnormality remained asymptomatic for venous thrombosis.

Two patients were reported to be symptomatic for cerebral thrombosis but no arteriographic studies were supplied (16). It is well known that vascular abnormalities and/or lipid metabolism alterations are frequent causes of stroke. This factor becomes even more important if one takes into account the fact that both were young males and one had a patent foramen ovale (16). Furthermore, in two instances there was no thrombosis despite the pres-

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TABLE 1. *Main features of 18 patients with homozygous 3' untranslated region 20210 prothrombin abnormality asymptomatic or symptomatic for venous thrombosis reported in the literature*

	Sex, age	Cases	Prothrombin level	Symptomatic (S) or asymptomatic (A)	Associated congenital risk factors	Associated acquired risk factors
Poort et al. 1996 (1)	F, ?	1	Not reported	**S**	factor V Leiden (Heterozygous)	?
Howard et al., 1997 (10)	M, 24	1	Upper limit of normalcy	**S**	factor V Leiden (Heterozygous)	Immobilization
Kapur et al., 1997 (2)	M, 66	1	Not reported	**S**	Hyperhomo-cysteinemia	None
Arruda et al., 1997 (6)	M, 57	1	Not reported	**A**	None	None
Scott et al., 1997 (11)	F, 18	1	Elevated	**S**	None	Pregnancy
Zawadsky et al., 1998 (13)	M, 48	2	Not reported,	**S**	None	None
	F,30		elevated	**S**	None	None
Gonzales-Ordonez et al., 1998 (12)	M, 65	1	Elevated	**S**	None	Surgery
Alatri et al., 1998 (5)	M, 72	1	Not reported	**A**	None	Two surgical procedures
Kyrle et al., 1998 (14)	M, 56	2	Elevated	**S**	None	None
	F, 52		Elevated	**S**	None	Pregnancy
De Stefano et al., 1998 (16)	M, 26	2	Not reported	**A(*)**	None	None
	M, 26		Not reported	**A(*)**	None	
Ridker et al., 1999 (15)	?	1	Not reported	**A**	None None	None
Girolami et al., 1999 (4)	M, 29	2	Upper limit of normalcy slightly elevated	**A**	None	None
	F, 39			**A**	None	Oral contraceptives
Eikelboom et al., 1999 (3)	F, 66	2	Elevated	**S**	None	None
	M, 68		Elevated	**A**	None	None

* Patients were reported to have had ischemic stroke but no angiographic study of their cerebral circulation was supplied.

ence of an associated acquired condition (prolonged oral contraceptive therapy in one patient and two surgical procedures in another (4,5). Finally, some patients remained asymptomatic until an old age (3,5).

CONCLUSIONS

The previously discussed observations are significant, and therefore, one is justified in raising at least some doubts about the significance of this polymorphism. It is worth remembering that we are dealing with homozygous patients.

The presence of such a large number of asymptomatic or doubtfully symptomatic patients homozygous for the abnormality casts serious doubts as to the significance of this abnormality as a prothrombotic condition. Extreme caution is needed before jumping to the conclusion that one clotting defect is the cause of a given thrombotic manifestation. An association of two conditions in the same patient does not necessarily mean that a casual relationship exists between the two phenomena (17). The concomitant presence of acquired conditions do play a role and are often important and difficult to evaluate (18). It is therefore advisable to abstain from claims that appear unjustified. This is not intended to imply that the prothrombin abnormality is not important and worth studying. However, it probably represents only a mild prothrombotic state, particularly if associated with other congenital or acquired risk factors.

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