Combination of congenital coagulation disorders: Factor II gene mutation G20210A, Factor V Leiden gene mutation G1691A and Protein S deficiency. A family study

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The thromboembolic phenomenon is nowadays considered to be a multicausal disease, in which the fact of being the carrier of a congenital prothrombotic disorder is not the cause, but rather an additional risk factor in the onset of thrombosis occurring as the result of the sum of various risk factors. These factors are usually a combination of external circumstances (precipitating factors) and a predisposition to thrombosis in the patient, which may be either hereditary or acquired. The literature describes various combinations of congenital deficiencies in two or more natural coagulation inhibitors, as well as combinations of these deficiencies with Factor II and V mutations or combinations of mutations in these factors. In this article we describe an unusual family case with three associated congenital disorders, a coagulation inhibitor deficit and two associated mutations, leading to different thrombotic processes in different members of the same family. A thrombophilia study was carried out on a patient who presented an episode of thrombosis in the superior mesenteric vein, initially suspected after ultrasound examination of the abdomen and confirmed by exploratory laparotomy. The patient had antecedents of repetitive thrombophlebitis without having suffered any prior thromboembolic process . A family study was made of the patient's daughter, his sister and two of her children. After drawing up a clinical history, including possible precipitating risk factors and previous thromboembolic processes, an analytical study consisting of a haemogram, a coagulation study (PT, APTT, fibrinogen, antithrombin III, total, free and functional protein S, functional protein C, FII activity, APCR-V) and a genetic study were performed. Factor II (FII) activity was determined by means of a coagulometric method on an ACL 7000 Coagulation Analyzer (Izasa). As a consequence of an excess of Factor V-deficient plasma the activated protein C resistance ratio (APCR-V) was also determined on an ACL 7000 Coagulation Analyzer (Izasa) by measuring APTT prolongation. The relationship between the APTT of plasma containing FV-deficient plasma and non-FV-deficient plasma gives the ratio of the resistance to activation of protein C (standard R>2). The amount of free protein S was evaluated by turbidimetric immunoanalysis, that of functional protein S by a coagulometric method, and that of total antigenic protein S by enzyme immunoanalysis. A genetic study was carried out on the above-mentioned family members for the existence of prothrombin gene mutation G20210A and gene mutation G1691A (Factor V Leiden), both assays being performed using a real-time multiplex PCR system (Light Cycler, Roche Molecular Biochemicals) according to the method established by van der Bergh F et al..[1] Figure 1 shows the genotype observed in the family study. A coagulation study, which due to the underlying pathology was non-evaluable, was performed on the patient (I-1), a 60-year-old male who was being tested for thrombophilia as a result of a clinical episode of thrombosis. The genetic study revealed heterozygosis for both mutations assayed. The patient had been a smoker (20 cigarettes/day) since he was 20, but was neither hypertensive nor obese, and showed no dyslipemia. The results of the coagulation factor activity analysis and the genetic analysis of the various family members are shown in table 1. The presence of venous thromboembolism has been repeatedly associated in the literature with reduced inhibitor levels in the coagulation cascade or with increased levels of coagulation factors, the risk being greater when genetic defects are combined.[2] The case presented in this study is extremely unusual, due to the low prevalence of protein S deficiency, which in the absence of confirmed data has been estimated at 1.3 &endash; 5% of patients with venous thrombosis.[3] Factor V Leiden has a prevalence of 5% in the European population, whilst that of the prothrombin gene mutation G20120A is between 1 &endash; 4%.[3] Mesenteric vein thrombosis (MVT) is a serious thrombotic process that occurs only occasionally, and in which a high proportion (75%) of mutation has been observed, such as homozygosis of methylene tetrahydrofolate reductase for C677T, or heterozygosis for Factor V Leiden or prothrombin gene mutation G20210A, with a high proportion of patients (33%) having more than one mutation. The presence of these mutations leads to a higher risk of MVT, as is shown by the odds ratios of 4.52, 6.19 and 6.85 for C677T, Factor V Leiden and G20210A respectively, when comparing the prevalence of the mutations present in twelve patients with MTV with the prevalence of these same mutations in four hundred and thir-

Figure 1. Family tree showing the genotype for each member of the family. (*) thrombotic process observed. () factor II heterozygous. () factor V heterozygous. () protein S deficiency.

Table 1. Activity of coaugulation factors and genetic analysis of different family members. NE: non-evaluable

			S protein			Factor II		Factor V
Patient	Age (y)	Clinical Thrombosis Process	Free	Functional	Total	G20210 Mutation	Activity	Leiden
I-1	60	Mesenteric vein Thrombosis	NE	NE	NE	Heterozygous	NE	Heterozygous
I-2	46	Ileo-Femoral Thrombosis	44.3%	40.6%	57%	Heterozygous	113%	Heterozygous
II-1	30	Deep-Vein Thrombosis	42%	47.4%	41%	Heterozygous	106%	Negative
II-2	24	No	36.9%	47.4%	47%	Heterozygous	115%	Negative
II-3	19	No	36.9%	33%	49%	Heterozygous	108%	Heterozygous

ty-one healthy subjects with no previous family or personal history of thrombotic processes.[4] No data are at present available for the frequency of protein S deficiency in the general population. In this report we present a family case study in which the propositus was diagnosed with MVT, there being no previous mention in the bibliography of cases involving the simultaneous appearance of the three deficits described above. However, the combination of these three abnormalities cannot be specifically associated with MTV, since both the propositus' sister and daughter, who share the same abnormalities, have presented different thromboembolic processes. Family cases of three simultaneous deficiencies in different inhibitors and coagulation factors are extremely rare, only occurring in approximately 5% of patients.[5] A similar case, that of simultaneous Factor V Leiden and G20210A mutations combined with protein C deficiency in a 64 year-old patient with mesenteric vein thrombosis, has been described in the literature.[6] In the present case, we have a simultaneous deficiency of three elements: Factor V Leiden, prothrombin gene G20210A polymorphism, and type 1 protein S deficiency. Probably the patient in question presents a combination of the three abnormalities, but protein S deficiency could not be evaluated due to the anti-coagulation treatment that was being administered. Nevertheless, the fact that the combination of these three abnormalities has been shown to exist in his sister may well be indicative. The patient with thrombosis and multiple thrombophilia is currently undergoing anticoagulation treatment, whilst the other patients have been recommended to avoid precipitating factors, since for the purposes of the family study they are not currently receiving anticoagulation treatment.

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