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G20210A homozygosity in antiphospholipid syndrome secondary to systemic lupus erythematosus

We report the first case of systemic lupus erythematosus (SLE)-associated antiphospholipid syndrome in a young female homozygous for the G20210A allele in the prothrombin gene who developed an extensive venous thrombosis while taking oral contraceptives.

Sir,

The risk of deep venous thrombosis (DVT) is increased by conditions that cause hypercoagulability or venous stasis.[1] A variant of prothrombin (G20210A) represents the second most common genetic risk factor in Caucasians, after factor V Leiden.[2-7] The mechanism of thrombosis is probably related to the high amounts of thrombin generated.[2]

We report a case of a 28-year old woman who developed an extensive DVT after having taken oral contraceptives for one year. Venous ultrasonography demonstrated a femoral-iliac thrombosis with proximal extension to the common iliac vein. Past history was positive for oral ulcers and Raynaud's phenomenon, since she was a teenager. She reported photosensitivity lasting years, with an important episode on the scalp some months earlier: scarring lesions with atrophy and alopecia were still evident. Platelet count, partial thromboplastin and prothrombin time, antithrombin III and fibrinogen were normal. The patient was treated with continuous intravenous nonfractionated heparin infusions followed by oral warfarin for 7 months (INR = 3.0). During the follow up erythrocyte sedimentation rate and immunoglobulin levels were moderately increased and white cell count repeatedly low. Her immunologic profile showed positive antinuclear-antibodies, anti-DNA, SSA, anticardiolipin, anti-β_2GPI and C4 hypocomplementemia. A second set of tests a few months later confirmed the picture. The final diagnosis was DVT in a patient with APS and SLE.

The search for factor V Leiden was negative. Prothrombin G20210A was evaluated by PCR and Hind III digestion. The patient was a G20210A homozygote. Family members were asymptomatic and none had a history of thrombosis. Their genotypes are given in Figure 1.

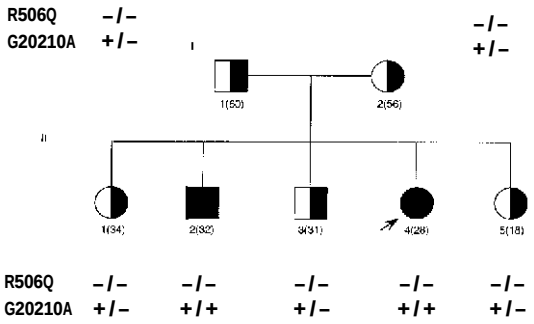

Figure 1. Pedigree of the family studied. The age of each subject is shown in brackets. The results of the mutations studied and their inheritance is indicated.

The G20210A mutation is associated with DVT with a 2.8 fold independent risk.[2] Homozygotes are rare; although they present the highest prothrombin activity values[8] data on their risk of thrombosis are controversial. This is not unexpected considering that a thrombotic event is the manifestation of a multifactorial disease.[1] The patient described here had two acquired factors associated with a genotype at risk: APS and oral contraceptives. The relative risk in women with factor V Leiden using contraceptives is 34.7; that of carriers of prothrombin variant is unknown.[1]

APS is characterized by venous and arterial thrombosis and often by recurrent fetal loss in the presence of lupus anticoagulant, anticardiolipin antibodies or both. It has been proposed that anti-β_2GPI, the presence of which correlates strongly with thrombosis, should be included in the APS biological score.[9] In APS associated with SLE the risk of DVT is enhanced by the possible vasculitis process inherent to disease activity. The frequency of factor II mutation is not expected to be increased in patients with APS but, in analogy to that which occurs for factor V Leiden,[10] when present may represent an independent risk factor for thrombosis.

The other members of the family had no history of DVT. The G20210A heterozygous parents are free of events, despite I-2 having had 5 pregnancies, a condition known to favor thrombosis. Neither has II-2, a G20210A homozygote, had any events, but this subject has never been exposed to risk situations.

In conclusion, our study suggests that the thrombotic risk in G20210A variant is mild and requires additional factors to become manifest.

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Key words

Thrombophilia, prothrombin variant, antiphospholipid syndrome, SLE

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Respiratory burst activity in late pregnancy in a carrier of X-linked chronic granulomatous disease

Screening for chronic granulomatous disease (CGD) and carrier status is carried out by the nitroblue tetrazolim test. The diagnosis is confirmed by quantitative tests of respiratory burst activity. Production of reactive oxygen intermediates may be increased in late pregnancy which may compensate for the otherwise low level in a CGD carrier, thus confounding diagnosis for the unwary clinician.

Sir,

We recently diagnosed chronic granulomatous disease (CGD) in a 6-year old boy who had a long history of recurrent bacterial and fungal infections involving the lung, liver and kidney. Diagnosis was made by counting nitroblue-tetrazolium (NBT)-reducing phagocytes (NBT slide test)[1] as well as by evaluating the oxidative burst activity by means of both SOD inhibitable Cytochrome c reduction (Cyt. c red.)[2] and flow cytometric (DCF fluorescence)[3] assays. To investigate the possibility of X-linked transmission we tested both his parents by means of the NBT slide test which revealed that ~70% of maternal neutrophils at 38 weeks of an uneventful gestation did not produce reactive oxygen intermediates after stimulation with either N-formyl-methionyl-leucyl-phenylalanine or phorbol myristate acetate. However, at the same stage of gestation, when the maternal neutrophils were analyzed by means of both Cyt. c red. and DCF fluorescence assays, no significant changes in the fMLP- or PMA-induced oxidative burst activity occurred compared to the changes found in a group of thirty randomly selected normal non-pregnant subjects. Repeat testing of the maternal neutrophils was performed five months after delivery of an apparently healthy female. Unanimously abnormal results obtained by the three tests were consistent with the diagnosis of carrier status. While the NBT-slide continued to show the same percentage of NBT-negative neutrophils, the amount of oxidative burst activity was 50 percent less than that recorded for neutrophils from control subjects (Table 1; Figure 1).

Although X-linked CGD carriers are usually healthy (as was our female case), with no manifestations of CGD, there are reports of a higher incidence of

Table 1. NBT slide test. Percentage of NBT non-responding cells.

Subjects	*Healthy donors*	*CGD-affected subjects*	*CGD carrier during pregnancy*	*CGD carrier 5 months after pregnancy*
% NBT non-responding cells	0-2	98-100	70-67	71-67

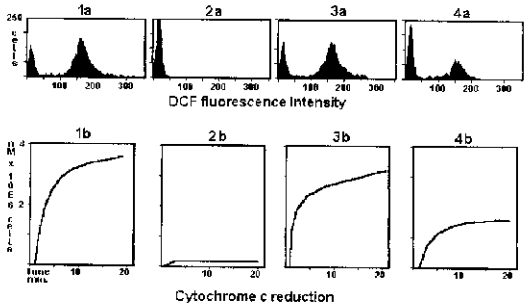

Figure 1. Evaluation of oxidative burst activity performed by flow cytometric assay (DCF fluorescence, and SOD inhibitable Cytochrome c reduction.