Venous thromboembolism in a young woman with combined homozygosity for Factor V Leiden and Prothrombin G20210A mutations

We report the unusual carriage of double homozygous factor V Leiden and factor II mutations, in a 22-year old woman presenting with an extensive proximal deep venous thrombosis involving left common and external iliac, femoro-politeal and infra-popliteal veins.

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Thrombophilia involves genetic and acquired conditions that increase the risk of venous thromboembolism (VTE). During the last decade, the identification of thrombophilic defects has increased from less than 10% to approximately 50% of patients presenting with unprovoked VTE.[1] The factor V Arg506Gln (factor V Leiden) and the prothrombin G20210A mutations are the most prevalent abnormalities, found in 15 to 25% and 6 to 16% of unselected VTE patients, respectively.[2] The severity of thrombophilic defects influences the individual VTE risk, the age at onset of disease and the rate of recurrence. Moreover, the clinical expression may differ between individuals bearing the same genetic background.

We report the unusual carriage of double homozygous factor V Leiden and factor II mutations, in a 22-year old woman presenting with an extensive proximal deep venous thrombosis involving left common and external iliac, femoro-politeal and infra-popliteal veins. The only precipitating factor was a third-generation oral contraceptive (Meliane®), begun six weeks earlier. No thrombotic event was documented among 5 first-degree relatives. No consanguinity was reported. Upon treatment with low molecular weight heparin relayed by acenocoumarol, the patient recovered uneventfully. No relapse occurred during a two-year observational period, with ongoing anticoagulation. The thrombophilia study revealed homozygosity for both factor V Arg506Gln (Leiden) and prothrombin 20210A mutations; no deficiency of protein C, S or antithrombin was found; plasma homocysteine level was normal; factor VIII-C was moderately increased to 179% of normal value, no antiphospholipid antibodies were found.

Table. A familial screening was performed (3):

	Clinical Event	*V Leiden*	*Prothrombin 20210A*	*MTHFR*
Propositus, 24 yr	*DVT (22 y)*	*+/+*	*+/+*	*+/-*
Father, 55 yr	*None*	*+/-*	*+/-*	*+/-*
Mother, 50 yr	*None*	*+/-*	*+/-*	*+/-*
Brother, 23 yr	*None*	*-/-*	*+/+*	*+/-*
Brother, 19 yr	*None*	*+/+*	*-/-*	*+/-*
Brother, 17 yr	*None*	*+/+*	*+/+*	*+/-*

+ : mutation present; - : mutation absent; ND : not done

Whereas the heterozygous carriage of factor V Leiden or prothrombin 20210A mutation is a moderate prothrombotic factor with an estimated relative VTE risk between 2 and 3, the homozygous carriage of one of these abnormalities or the double heterozygosity is a more severe thrombophilic condition.[2] In a study that pooled 8 case-control studies, the odds ratio for VTE was 9,85 for carriers of homozygous factor V Leiden and 20 for carriers of double heterozygous factor V Leiden and factor II mutations.[2] In double heterozygous patients, the first episode occurred at a significantly younger age.

Due to an estimated prevalence of 0,02% for homozygous factor V Leiden and 0,014% for homozygous prothrombin 20210A mutation, the expected prevalence of double homozygosity is extremely rare, around 3 per 100 millions. Unsofar, double homozygous factor V and prothrombin mutations have been reported in 3 patients with unprovoked thrombosis, 9, 18 and 34-year old, respectively.[4-6] The current case was characterized by the occurrence of an extended deep venous thrombosis, very soon after starting a third-generation contraceptive. After a protracted debate, third-generation contraceptives are presently considered as more thrombogenic than second-generation preparations.[7] Surprisingly, no thrombotic event occurred among the 4 relatives who were double heterozygous or homozygous for one mutation, nor in a 17-year brother who was also homozygous for the factor V and factor II mutations. Third generation pill had double the risk of thrombosis of second generation pills and was obviously in this case a strong precipitating factor. Nevertheless, the variability of clinical expression among individuals bearing the same thrombophilic defects could suggest the intervention of additional protective or thrombogenic factors.

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